

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 16 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

**In The claims:**

Please amend the claims as indicated below.

CLAIMS 1-568 (PREVIOUSLY CANCELLED).

Claim 569 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising ~~the steps of~~ :

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising : (a) a sequence complementary to said nucleic acid of interest or to a portion thereof ; ~~wherein each of said fragments comprises~~ and (b) one or more detectable non-radioactively modified or labeled nucleotides or detectable non-radioactively modified or labeled nucleotide analogs, provided that said nucleotide analogs can be incorporated within, or onto a terminus of, said fragments without substantially interfering with the ability of said fragments to hybridize to the nucleic acid of interest or portion thereof, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~one or more detectable non-radioactively~~ modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar furanose moiety, the sugar analog, the phosphate moiety, the phosphate analog, or the base moiety ; or the base analog thereof ;

subjecting said ~~detectable non-radioactively labeled~~ fragments to a sequencing gel to separate or resolve said fragments; ~~and~~

detecting non-radioactively the presence of each of said separated or resolved fragments by detecting the ~~by means of said detectable non-radioactively~~ modified or labeled nucleotides or nucleotide analogs that are incorporated within, or onto a terminus of, said fragments ; ; and

determining the sequence of said nucleic acid of interest.

Claim 570 (PREVIOUSLY PRESENTED). The process according to claim 569, wherein the nucleic acid sequence of interest is derived from an organism.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 17 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 571 (PREVIOUSLY PRESENTED). The process according to claim 570, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 572 (PREVIOUSLY PRESENTED). The process according to claim 571, wherein said organism comprises a mammal.

Claim 573 (PREVIOUSLY PRESENTED). The process according to claim 572, wherein said mammal comprises a human being.

Claim 574 (PREVIOUSLY PRESENTED). The process according to claim 570, wherein said organism is living.

Claim 575 (PREVIOUSLY PRESENTED). The process according to claims 570 or 574, wherein said organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 576 (PREVIOUSLY PRESENTED). The process according to claim 575, wherein said organism comprises a eukaryote.

Claim 577 (PREVIOUSLY PRESENTED). The process according to claim 576, wherein said eukaryotic nucleic acid sequence of interest is contained within a chromosome.

Claim 578 (PREVIOUSLY PRESENTED). The process according to claim 576, wherein said eukaryote comprises a mammal.

Claim 579 (PREVIOUSLY PRESENTED). The process according to claim 578, wherein said mammalian nucleic acid sequence of interest is contained within a chromosome.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 18 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 580 (PREVIOUSLY PRESENTED). The process according to claim 578, wherein said mammal comprises a human being.

Claim 581 (PREVIOUSLY PRESENTED). The process according to claim 580, wherein said human nucleic acid sequence of interest is contained within a chromosome.

Claim 582 (PREVIOUSLY PRESENTED). The process according to claim 581, wherein said human chromosomal nucleic acid sequence of interest is part of a human gene library.

Claim 583 (CURRENTLY AMENDED). The process according to claim 569, wherein said modified or labeled nucleotides or nucleotide analogs are incorporated within, or onto a terminus of, said fragments with an enzyme in said providing or generating step ~~the fragments are provided or generated by one or more primers, nucleoside triphosphates or analogs thereof, or a combination thereof.~~

Claim 584 (CURRENTLY AMENDED). The process according to claim 583, wherein said modified or labeled nucleotides or nucleotide analogs comprise said nucleoside triphosphates ~~are~~ selected from the group consisting of ribonucleoside triphosphates, deoxyribonucleoside triphosphates, dideoxyribonucleoside triphosphates, and analog ~~analog~~ a combination of any of the foregoing.

Claim 585 (PREVIOUSLY PRESENTED). The process according to claim 569, wherein said fragments have been obtained or generated by a nucleic acid sequencing step or technique.

Claim 586 (CURRENTLY AMENDED). The process according to claim 569, wherein the detectable non-radioactively labeled ~~complementary~~ nucleic acid fragments ~~is fragmented~~ hybridize to the nucleic acid of interest or to a portion thereof prior to separation in said sequencing gel.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 19 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 587 (CURRENTLY AMENDED). The process according to claim 569, wherein before or during said providing or generating step, at least one of the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs ~~are have been~~ incorporated ~~into~~ at a terminus of at least one of said nucleic acid fragment or fragments.

Claim 588 (CURRENTLY AMENDED). The process according to claim ~~587~~ 583, wherein at least one of said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs is incorporated at a terminus of at least one of said fragment or fragments.

Claim 589 (CURRENTLY AMENDED). The process according to claim 588, wherein said ~~terminus comprises the 5' or the 3' terminus~~ enzyme is a terminal transferase.

Claim 590 (CURRENTLY AMENDED). The process according to claim ~~587~~ 588, wherein ~~said incorporation has been carried out in the presence of a primer~~ the enzyme is a ligase.

Claim 591 (CURRENTLY AMENDED). The process according to claim ~~569~~ 588, wherein said ~~nucleotide analog can be attached terminally to DNA or RNA by means of an enzyme~~ is a polymerase.

Claim 592 (CURRENTLY AMENDED). The process according to claim ~~591~~ 569, wherein ~~said enzyme comprises terminal transferase~~ at least one of said modified or labeled nucleotides or nucleotide analogs is incorporated onto a terminus of said fragments through chemical coupling.

Claim 593 (CURRENTLY AMENDED). The process according to claim 592, wherein said chemical coupling is carried out with carbodiimide or formaldehyde ~~569, wherein said nucleotides or nucleotide analog can be coupled to the DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.~~

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 20 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 594 (CURRENTLY AMENDED). The process according to claim 593, ~~wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde~~ 587, 588 or 592, wherein said terminus is a 3' terminus.

Claim 595 (CURRENTLY AMENDED). The process according to claim ~~593,~~ 587, 588 or 592, wherein ~~enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase~~ said terminus is a 5' terminus.

Claim 596 (PREVIOUSLY CANCELLED).

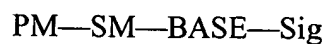
Claim 597 (PREVIOUSLY PRESENTED). The process according to claim 569 or 596, wherein, said incorporation is carried out by means of a polymerizing enzyme.

Claim 598 (PREVIOUSLY PRESENTED). The process according to claim ~~597,~~ wherein said polymerizing enzyme comprises a polymerase.

Claim 599 (PREVIOUSLY PRESENTED). The process according to claim 598, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 600 (CURRENTLY AMENDED). The process according to claim 569, wherein at said providing or generating step, the ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

**Enz-5(D8)(C2)**

PM is a phosphate moiety ~~or phosphate analog~~ ,

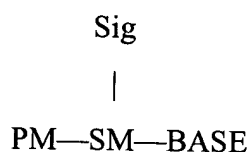
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety ~~or a base analog of any of the foregoing~~; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

(ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

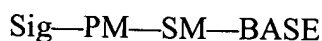
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide structure or nucleotide analog structure ~~, said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~ ,

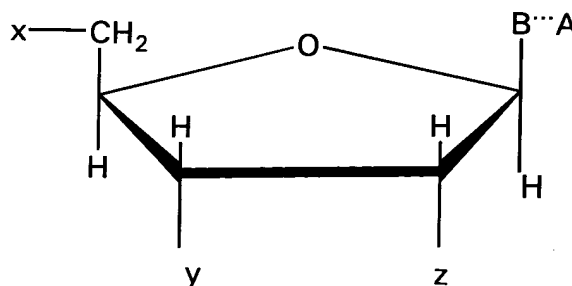
BASE is a base moiety ~~or base analog~~ , and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

Claim 601 (CURRENTLY AMENDED). The process according to claim 569, wherein at said providing or generating step, the ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, or a pyrimidine moiety, ~~or an analog of any of the foregoing~~, and B is covalently bonded to the C1' position of the ~~sugar~~ furanose moiety ~~or sugar analog~~, provided that whenever B is a purine, ~~a purine analog~~, or a 7-deazapurine moiety ~~or a 7-deazapurine analog~~, the ~~sugar~~ furanose moiety ~~or sugar analog~~ is attached at the N9 position of the purine moiety, ~~the purine analog~~, or the 7-deazapurine moiety ~~or the 7-deazapurine analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the ~~sugar~~ furanose moiety ~~or sugar analog~~ is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

Dean L. Engelhardt et al.

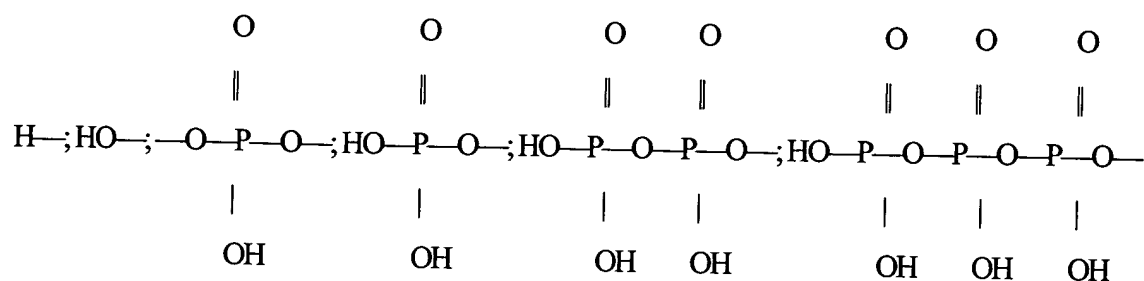
Serial No.: 08/486,069

Filed: June 7, 1995

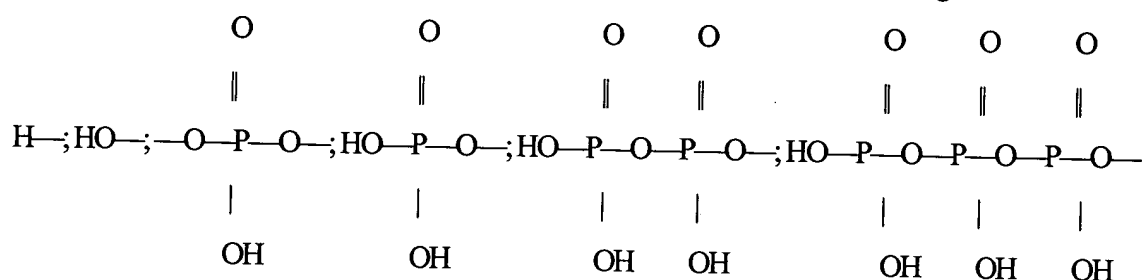
**Page 23 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

wherein B and A are covalently attached directly or through a linkage group,  
wherein if B is a purine ~~or a purine analog~~, A is attached to the 8-position of the purine ~~or purine analog~~, if B is a 7-deazapurine ~~or 7-deazapurine analog~~, A is attached to the 7-position of the deazapurine ~~or deazapurine analog~~, and if B is a pyrimidine ~~or a pyrimidine analog~~, A is attached to the 5-position of the pyrimidine ~~or pyrimidine analog~~; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H— and HO—.

Claim 602 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein y and z are H—.

Claim 603 (CURRENTLY AMENDED). The process according to claim ~~569~~ 600, wherein said PM phosphate moiety or phosphate analog is selected from the group consisting of a mono-phosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 604 (CURRENTLY AMENDED). The process according to claim 600, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises a nucleoside mono-, di- or tri-phosphate.

Claim 605 (CURRENTLY AMENDED). The process according to claims ~~569 or~~ 600, wherein said ~~sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 25 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 606. (CURRENTLY CANCELLED) The process according to claim 605, wherein said monosaccharide comprises a furanose.

Claim 607 (CURRENTLY AMENDED). The process according to claim ~~606~~ 600 , wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 608 (CURRENTLY AMENDED). The process according to claim 600, wherein ~~said base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 609 (CURRENTLY CANCELLED). The process according to claim 600, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

Claim 610 (CURRENTLY AMENDED). The process according to claim 600, wherein said modified or labeled nucleotides or nucleotide analogs comprise nucleotide or nucleotide analog structure (i) and said Sig detectable non-radioactive moiety in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position , when BASE is a purine , that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 611 (CURRENTLY AMENDED). The process according to claim 600, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

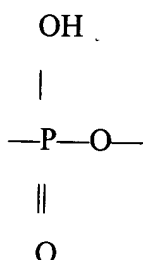
**Page 26 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

Claim 612 (CURRENTLY AMENDED). The process according to claim 606, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to ~~furanose~~ SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 613 (CURRENTLY AMENDED). The process according to claim 606, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 614 (CURRENTLY AMENDED) The process according to claim 600, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



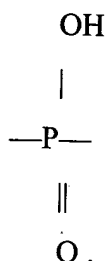
Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 27 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

and



Claim 615 (CURRENTLY AMENDED). The process according to claim 600, wherein PM is a mono-, di- or tri-phosphate, and wherein in said nucleotide or nucleotide analog structure (iii), the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

Claim 616 (CURRENTLY AMENDED). The process according to claim 600, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

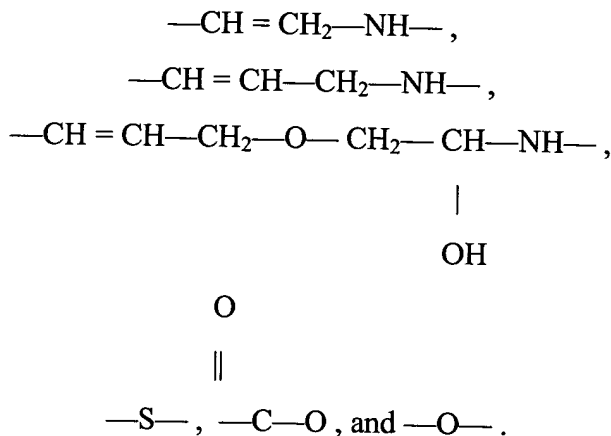
Claim 617 (CURRENTLY AMENDED). The process according to claim 600, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of: a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i), a —CH<sub>2</sub>NH— moiety, or both.

Claim 618 (CURRENTLY AMENDED). The process according to claim 600, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 619 (CURRENTLY AMENDED). The process according to claim 600, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i),~~



(ii) or (iii) comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 620 (CURRENTLY AMENDED). The process according to claim 600, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Claim 621 (CURRENTLY AMENDED). The process according to claim 600, wherein in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) , said Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 622 (CURRENTLY AMENDED). The process according to claim 621, wherein , in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 623 (PREVIOUSLY PRESENTED). The process according to claim 622, wherein said amine comprises a primary amine.

Claim 624 (PREVIOUSLY PRESENTED). The process according to claim 621, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

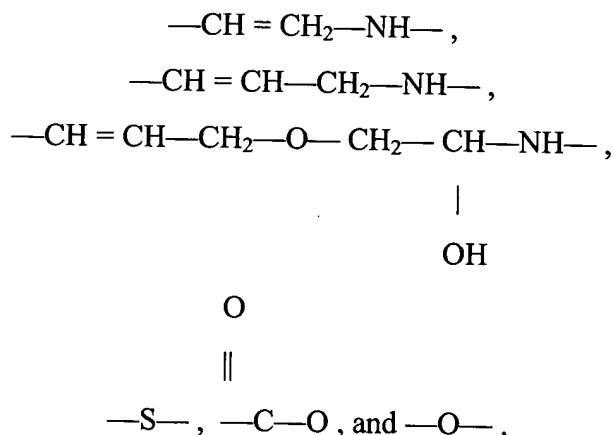
**Page 29 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 625 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein said covalent attachment does not interfere substantially with the characteristic ability of A to form a detectable non-radioactive signal.

Claim 626 (CURRENTLY AMENDED). The process according to claim 601, wherein said covalent attachment comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 627 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein said covalent attachment comprises an allylamine group.

Claim 628 (CURRENTLY AMENDED). The process according to claim 601, wherein said covalent attachment comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 629 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein said covalent attachment includes a glycosidic linkage moiety.

Claim 630 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein said A is covalently attached to B through a linkage group.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 30 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 631 (PREVIOUSLY PRESENTED). The process according to claim 630, wherein said linkage group contains an amine.

Claim 632 (PREVIOUSLY PRESENTED). The process according to claim 631, wherein said amine comprises a primary amine.

Claim 633 (PREVIOUSLY PRESENTED). The process according to claim 630, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 634 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein Sig comprises at least three carbon atoms.

Claim 635 (CURRENTLY AMENDED). The process according to claim 600, wherein said Sig ~~detectable non-radioactive moiety~~ comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 636 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 637 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic moiety comprising at least five carbon atoms.

Claim 638 (PREVIOUSLY PRESENTED). The process according to claim 637, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 31 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 639 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 640 (PREVIOUSLY PRESENTED). The process according to claim 639, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 641 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 642 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component or a chelating component.

Claim 643 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises an electron dense component.

Claim 644 (PREVIOUSLY CANCELLED).

Claim 645 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a magnetic component.

Claim 646 (PREVIOUSLY PRESENTED). The process according to claim 645, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 647 (PREVIOUSLY CANCELLED).

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 32 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 648 (PREVIOUSLY PRESENTED). The process according to claim 600, wherein Sig comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 649 (PREVIOUSLY PRESENTED). The process according to claim 648, wherein the binding protein comprises a lectin.

Claim 650 (PREVIOUSLY PRESENTED). The process according to claim 649, wherein the lectin comprises concanavalin A.

Claim 651 (PREVIOUSLY PRESENTED). The process according to claim 649, wherein said lectin is conjugated to ferritin.

Claim 652 (PREVIOUSLY CANCELLED).

Claim 653 (PREVIOUSLY CANCELLED).

Claim 654 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a hormone.

Claim 655 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a metal-containing component.

Claim 656 (PREVIOUSLY PRESENTED). The process according to claim 655, wherein said metal-containing component is catalytic.

Claim 657 (CURRENTLY AMENDED). The process according to claim 600, wherein ~~said Sig detectable non-radioactive moiety~~ comprises ~~an~~ a non-radioactively detectable indicator molecule moiety.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 33 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 658 (CURRENTLY AMENDED). The process according to claim 657, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 659 (CURRENTLY AMENDED). The process according to claim 658, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 660 (CURRENTLY AMENDED). The process according to claim 659, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 661 (CURRENTLY AMENDED). The process according to claim 660, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 662 (CURRENTLY AMENDED). The process according to claim 661, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 663 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a fluorescent component.

Claim 664 (PREVIOUSLY PRESENTED). The process according to claim 663, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 665 (PREVIOUSLY PRESENTED). The process according to claim 664, wherein said fluorescent component comprises fluorescein.

Claim 666 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a chemiluminescent component.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 34 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 667 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 668 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises an antibody component.

Claim 669 (PREVIOUSLY PRESENTED). The process according to claim 642, wherein Sig comprises a chelating component.

Claim 670 (CURRENTLY AMENDED). The process according to claim 657, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 671 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 672 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 673 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 674 (PREVIOUSLY PRESENTED). The process according to claim 673, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 35 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 675 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 676 (PREVIOUSLY PRESENTED). The process according to claim 675, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 677 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 678 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 679 (PREVIOUSLY PRESENTED). The process according to claim 678, wherein A comprises an electron dense component.

Claim 680 (PREVIOUSLY CANCELLED)

Claim 681 (PREVIOUSLY PRESENTED). The process according to claim 678, wherein A comprises a magnetic component.

Claim 682 (PREVIOUSLY PRESENTED). The process according to claim 681, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 684 (PREVIOUSLY PRESENTED). The process according to claim 601, wherein A comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 36 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 685 (PREVIOUSLY PRESENTED). The process according to claim 684, wherein the binding protein comprises a lectin.

Claim 686 (PREVIOUSLY PRESENTED). The process according to claim 685, wherein the lectin comprises concanavalin A.

Claim 687 (PREVIOUSLY PRESENTED). The process according to claim 685, wherein said lectin is conjugated to ferritin.

Claim 688 (PREVIOUSLY CANCELLED).

Claim 689 (PREVIOUSLY CANCELLED).

Claim 690 (PREVIOUSLY PRESENTED). The process according to claim 678, wherein A comprises a hormone.

Claim 691 (PREVIOUSLY PRESENTED). The process according to claim 678, wherein A comprises a metal-containing component.

Claim 692 (PREVIOUSLY PRESENTED). The process according to claim 691, wherein said metal-containing component is catalytic.

Claim 693 (CURRENTLY AMENDED). The process according to claim 601, wherein said A comprises ~~an~~ a non-radioactively detectable indicator molecule moiety.

Claim 694 (CURRENTLY AMENDED). The process according to claim 693, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 37 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 695 (CURRENTLY AMENDED). The process according to claim 694, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 696. (CURRENTLY AMENDED). The process according to claim 695, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 697 (CURRENTLY AMENDED). The process according to claim 696, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 698 (CURRENTLY AMENDED). The process according to claims 696 or 697, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 699 (PREVIOUSLY PRESENTED). The process according to claim 678, wherein A comprises a fluorescent component.

Claim 700 (PREVIOUSLY PRESENTED). The process according to claim 699, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 701 (PREVIOUSLY AMENDED). The process according to claim 700, wherein said fluorescent component comprises fluorescein.

Claim 702 (PREVIOUSLY AMENDED). The process according to claim 678, wherein A comprises a chemiluminescent component.

Claim 703 (PREVIOUSLY AMENDED). The process according to claim 678, wherein A comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 38 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 704 (PREVIOUSLY AMENDED). The process according to claim 678, wherein A comprises an antibody component.

Claim 705 (PREVIOUSLY AMENDED). The process according to claim 678, wherein A comprises a chelating component.

Claim 706 (CURRENTLY AMENDED). The process according to claim 693, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 707 (PREVIOUSLY AMENDED). The process according to claim 569, wherein said labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

Claim 708 (PREVIOUSLY AMENDED). The process according to claim 569, wherein said subjecting step is carried out electrophoretically.

Claim 709 (PREVIOUSLY AMENDED). The process according to claims 569, 600 or 601, wherein said detecting step is carried out directly.

Claim 710 (CURRENTLY AMENDED). The process according to claim 709, wherein the labeled fragments comprise one or more non-radioactively detectable indicator moieties and said direct detection is carried out using ~~one or more~~ these indicator ~~molecules~~ moieties.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 39 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 711 (CURRENTLY AMENDED). The process according to claim 710, wherein said ~~one or more~~ non-radioactively detectable indicator ~~molecules~~ moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~.

Claim 712 (CURRENTLY AMENDED). The process according to claim 711, wherein said ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Claim 713 (CURRENTLY AMENDED). The process according to claim 709, wherein said detecting step is carried out by means of a directly detectable signal provided by said ~~one or more~~ non-radioactively modified or labeled nucleotides or nucleotide analogs, ~~said A or said Sig~~ detectable non-radioactive moiety.

Claim 714 (CURRENTLY AMENDED). The process according to claim 713, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating ~~compound~~ structure, a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 715 (PREVIOUSLY CANCELLED).

Claim 716 (CURRENTLY AMENDED). The process according to claims ~~569~~, 600 or 601, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said ~~one or more~~ non-radioactively modified or labeled nucleotides or nucleotide analogs, ~~said A or said Sig~~ detectable non-radioactive moiety.

Claim 717 (PREVIOUSLY PRESENTED). The process according to claim 716, wherein in said detecting step the indirectly detectable signal is selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 40 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 718 (PREVIOUSLY CANCELLED).

Claim 719 (PREVIOUSLY PRESENTED). The process according to claim 569, wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs are capable of being detected non-radioactively by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 720 (PREVIOUSLY PRESENTED). The process according to claim 569, wherein said detecting step comprises localizing said non-radioactively labeled nucleic acid fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs.

Claim 721 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising the steps of :

providing or generating detectable non-radioactive non-radioactively-labeled nucleic acid fragments that are non-radioactively labeled , each fragment comprising : (a) a sequence complementary to said nucleic acid of interest or to a portion thereof and (b) one or more detectable non-radioactively modified or labeled nucleotides or detectable non-radioactively modified or labeled nucleotide analogs, provided that said modified or labeled nucleotide analogs can be attached to said fragments or incorporated within or onto a terminus of said fragments without substantially interfering with the ability of said fragments to hybridize to the nucleic acid of interest or portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar furanose moiety, the sugar analog, the phosphate moiety, the phosphate analog, or the base moiety, or the base analog thereof ;

introducing or subjecting said ~~detectable non-radioactively-labeled~~ fragments to a sequencing gel;

**Enz-5(D8)(C2)**

separating or resolving said fragments in said sequencing gel; and  
detecting non-radioactively each of the separated or resolved fragments; and  
determining the sequence of said nucleic acid of interest.

Claim 722 (PREVIOUSLY AMENDED). The process according to claim 721, wherein the nucleic acid sequence of interest is derived from an organism.

Claim 723 (PREVIOUSLY PRESENTED). The process according to claim 722, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 724 (PREVIOUSLY PRESENTED). The process according to claim 723, wherein said organism comprises a mammal.

Claim 725 (PREVIOUSLY PRESENTED). The process according to claim 724, wherein said mammal comprises a human being.

Claim 726 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said organism is living.

Claim 727 (PREVIOUSLY PRESENTED). The process according to claims 722 or 726, wherein said organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 728 (PREVIOUSLY PRESENTED). The process according to claim 727, wherein said organism comprises a eukaryote.

Claim 729 (PREVIOUSLY PRESENTED). The process according to claim 728, wherein said eukaryotic nucleic acid sequence of interest is contained within a chromosome.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 42 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 730 (PREVIOUSLY PRESENTED). The process according to claim 728, wherein said eukaryote comprises a mammal.

Claim 731 (PREVIOUSLY PRESENTED). The process according to claim 730, wherein said mammalian nucleic acid sequence of interest is contained within a chromosome.

Claim 732 (PREVIOUSLY PRESENTED). The process according to claim 730, wherein said mammal comprises a human being.

Claim 733 (PREVIOUSLY PRESENTED). The process according to claim 732, wherein said human nucleic acid sequence of interest is contained within a chromosome.

Claim 734 (PREVIOUSLY PRESENTED). The process according to claim 733, wherein said human chromosomal nucleic acid sequence of interest is part of a human gene library.

Claim 735 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein in said providing or generating step the fragments are provided or generated by one or more primers, or nucleoside triphosphates ~~or analogs thereof~~, or a combination thereof.

Claim 736 (PREVIOUSLY PRESENTED). The process according to claim 735, wherein said nucleoside triphosphates are selected from the group consisting of ribonucleoside triphosphates, deoxyribonucleoside triphosphates, dideoxyribonucleoside triphosphates, and ~~analog~~s a combination of any of the foregoing.

Claim 737 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said fragments have been obtained or generated by a nucleic acid sequencing step or technique.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 43 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 738 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

Claim 739 (CURRENTLY AMENDED). The process according to claim 721, wherein at said providing or generating step, the ~~one or more non-radioactively~~ modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

Claim 740 (CURRENTLY AMENDED). The process according to claim 739, wherein at least one of said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

Claim 741 (PREVIOUSLY PRESENTED). The process according to claim 740, wherein said terminus comprises the 5' or the 3' terminus.

Claim 742 (PREVIOUSLY PRESENTED). The process according to claim 739, wherein said incorporation has been carried out in the presence of a primer.

Claim 743 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said nucleotide analog can be attached terminally to DNA or RNA by means of an enzyme.

Claim 744 (PREVIOUSLY PRESENTED). The process according to claim 743, wherein said enzyme comprises terminal transferase.

Claim 745 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said nucleotide analog can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 44 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 746 (PREVIOUSLY PRESENTED). The process according to claim 745, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 747 (PREVIOUSLY PRESENTED). The process according to claim 745, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.

Claim 748 (PREVIOUSLY CANCELLED).

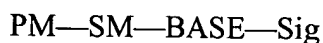
Claim 749 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 750 (PREVIOUSLY PRESENTED). The process according to claim 749, wherein said polymerizing enzyme comprises a polymerase.

Claim 751 (PREVIOUSLY PRESENTED). The process according to claim 750, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 752 (CURRENTLY AMENDED). The process according to claim 721, wherein at said providing or generating step, the ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

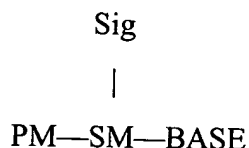
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

**Enz-5(D8)(C2)**

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety ~~or a base analog of any of the foregoing~~; and

Sig is a detectable non-radioactive moiety,  
wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

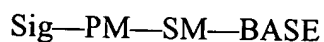
SM is a sugar-furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure ~~, said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose ~~moiety or sugar analog~~,

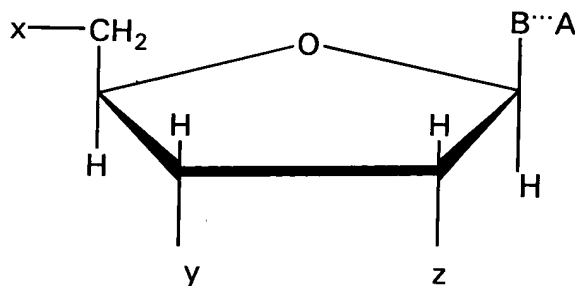
BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

Claim 753 (CURRENTLY AMENDED). The process according to claim 721, wherein in said providing or generating step, the ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the ~~sugar~~ furanose ~~moiety or sugar analog~~, provided that whenever B is a purine, a ~~purine analog~~, a 7-deazapurine moiety ~~or a 7-deazapurine analog~~, the ~~sugar~~ furanose ~~moiety or sugar analog~~ is attached at the N9 position of the purine moiety, ~~the purine analog~~, or of the 7-deazapurine moiety ~~or the 7-deazapurine analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the ~~sugar~~ furanose ~~moiety or sugar analog~~ is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

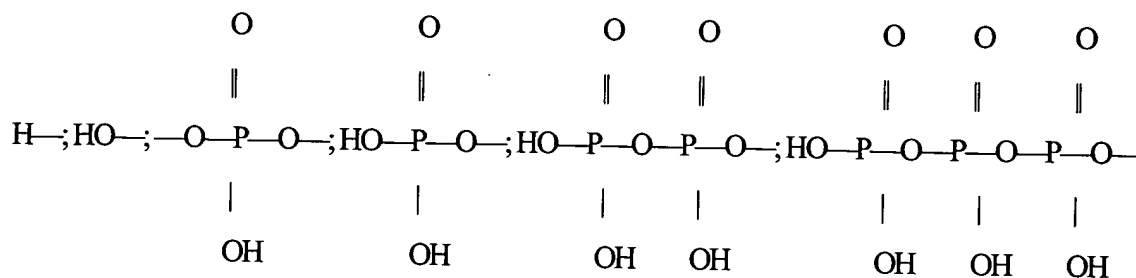
**Page 47 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

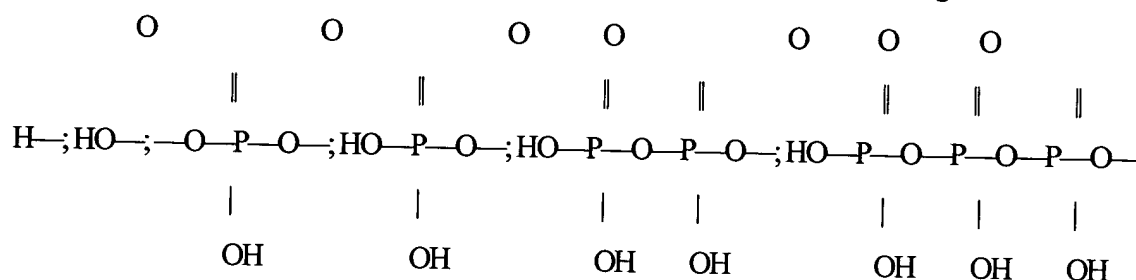
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine ~~or a purine analog~~, A is attached to the 8-position of the purine ~~or purine analog~~, if B is a 7-deazapurine ~~or 7-deazapurine analog~~, A is attached to the 7-position of the deazapurine ~~or deazapurine analog~~, and if B is a pyrimidine ~~or a pyrimidine analog~~, A is attached to the 5-position of the pyrimidine ~~or pyrimidine analog~~; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO-.

Claim 754 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein y and z are H-.

Claim 755 (CURRENTLY AMENDED). The process according to claim 721, wherein said PM ~~phosphate moiety or phosphate analog~~ is selected from the group consisting of a mono-phosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 756 (CURRENTLY AMENDED). The process according to claim 752, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises a nucleoside mono-, di- or tri-phosphate.

Claim 757 (CURRENTLY AMENDED). The process according to claims 721 or 752, wherein said ~~sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 49 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 758. (CURRENTLY CANCELLED) The process according to claim 757, wherein said monosaccharide comprises a furanose.

Claim 759 (CURRENTLY AMENDED). The process according to claim ~~758~~ 721 or 752 , wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 760 (CURRENTLY AMENDED). The process according to claim 752, wherein ~~said base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 761 (CURRENTLY CANCELLED). The process according to claim 752, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

Claim 762 (CURRENTLY AMENDED). The process according to claim 752, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position when BASE is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 763 (CURRENTLY AMENDED). The process according to claim 752, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

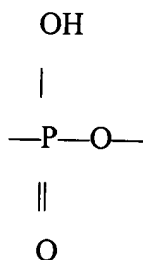
**Page 50 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

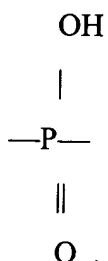
Claim 764 (CURRENTLY AMENDED). The process according to claim 758, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 765 (CURRENTLY AMENDED). The process according to claim 758, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 766 (CURRENTLY AMENDED). The process according to claim 752, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



and



Claim 767 (CURRENTLY AMENDED). The process according to claim 752, wherein PM is a mono-, di or tri-phosphate, and wherein said nucleotide or nucleotide analog structure (iii), the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

Claim 768 (CURRENTLY AMENDED). The process according to claim 752, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 769 (CURRENTLY AMENDED). The process according to claim 752, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a —CH<sub>2</sub>NH— moiety, or both.

Claim 770 (CURRENTLY AMENDED). The process according to claim 752, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 771 (CURRENTLY AMENDED). The process according to claim 752, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i),~~



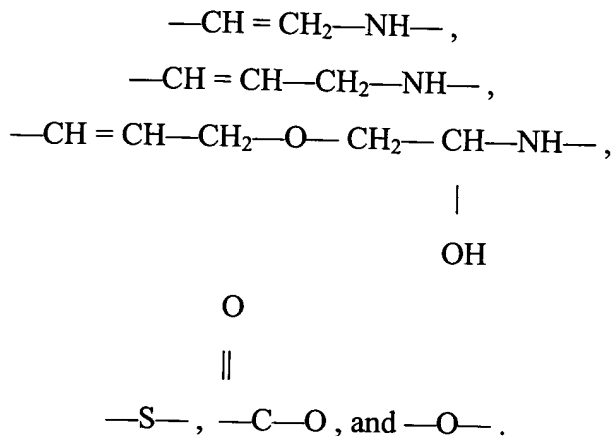
Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 52 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

~~(ii) or (iii)~~ comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 772 (CURRENTLY AMENDED). The process according to claim 752, wherein in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Claim 773 (CURRENTLY AMENDED). The process according to claim 752, wherein in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) said Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 774 (CURRENTLY AMENDED). The process according to claim 773, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 775 (PREVIOUSLY PRESENTED). The process according to claim 774, wherein said amine comprises a primary amine.

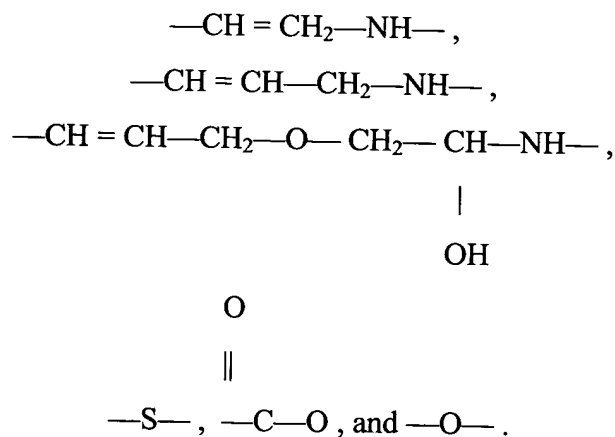
Claim 776 (PREVIOUSLY PRESENTED). The process according to claim 773, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 777 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein said covalent attachment does not interfere substantially with the characteristic ability of A to form a detectable non-radioactive signal.

Claim 778 (CURRENTLY AMENDED). The process according to claim 753, wherein said covalent attachment comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 779 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein said covalent attachment comprises an allylamine group.

Claim 780 (CURRENTLY AMENDED). The process according to claim 753, wherein said covalent attachment comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 781 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein said covalent attachment includes a glycosidic linkage moiety.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 54 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 782 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein said A is covalently attached to B through a linkage group.

Claim 783 (PREVIOUSLY PRESENTED). The process according to claim 782, wherein said linkage group contains an amine.

Claim 784 (PREVIOUSLY PRESENTED). The process according to claim 783, wherein said amine comprises a primary amine.

Claim 785 (PREVIOUSLY PRESENTED). The process according to claim 782, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 786 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein Sig comprises at least three carbon atoms.

Claim 787 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 788 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 789 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic moiety comprising at least five carbon atoms.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 55 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 790 (PREVIOUSLY PRESENTED). The process according to claim 789, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 791 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 792 (PREVIOUSLY PRESENTED). The process according to claim 791, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 793 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 794 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 795 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises an electron dense component.

Claim 796 (PREVIOUSLY PRESENTED). The process according to claim 795, wherein said electron dense component comprises ferritin.

Claim 797 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a magnetic component.

Claim 798 (PREVIOUSLY CANCELLED).

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 56 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 799 (PREVIOUSLY CANCELLED).

Claim 800 (PREVIOUSLY PRESENTED). The process according to claim 752, wherein Sig comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 801 (PREVIOUSLY PRESENTED). The process according to claim 800, wherein the binding protein comprises a lectin.

Claim 802 (PREVIOUSLY PRESENTED). The process according to claim 801, wherein the lectin comprises concanavalin A.

Claim 803 (PREVIOUSLY PRESENTED). The process according to claim 801, wherein said lectin is conjugated to ferritin.

Claim 804 (PREVIOUSLY CANCELLED).

Claim 805 (PREVIOUSLY CANCELLED).

Claim 806 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a hormone.

Claim 807 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a metal-containing component.

Claim 808 (PREVIOUSLY PRESENTED). The process according to claim 807, wherein said metal-containing component is catalytic.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 57 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 809. (CURRENTLY AMENDED) The process according to claim 752, wherein said Sig ~~detectable non-radioactive moiety~~ comprises an a non-radioactively detectable indicator ~~molecule~~ moiety.

Claim 810 (CURRENTLY AMENDED). The process according to claim 809, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 811 (CURRENTLY AMENDED). The process according to claim 810, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 812 (CURRENTLY AMENDED). The process according to claim 811, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 813 (CURRENTLY AMENDED). The process according to claim 812, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 814 (CURRENTLY AMENDED). The process according to claim 813, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 815 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a fluorescent component.

Claim 816 (PREVIOUSLY PRESENTED). The process according to claim 815, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 817 (PREVIOUSLY PRESENTED). The process according to claim 816, wherein said fluorescent component comprises fluorescein.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 58 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 818 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a chemiluminescent component.

Claim 819 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 820 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises an antibody component.

Claim 821 (PREVIOUSLY PRESENTED). The process according to claim 794, wherein Sig comprises a chelating component.

Claim 822 (CURRENTLY AMENDED). The process according to claim 809, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 823 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 824 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 825 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 59 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 826 (PREVIOUSLY PRESENTED). The process according to claim 825, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 827 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 828 (PREVIOUSLY PRESENTED). The process according to claim 827, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 829 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 830 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 831 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises an electron dense component.

Claim 832 (PREVIOUSLY CANCELLED).

Claim 833 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a magnetic component.

Claim 834 (PREVIOUSLY PRESENTED). The process according to claim 833, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 60 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 835 (PREVIOUSLY CANCELLED).

Claim 836 (PREVIOUSLY PRESENTED). The process according to claim 753, wherein A comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 837 (PREVIOUSLY PRESENTED). The process according to claim 836, wherein the binding protein comprises a lectin.

Claim 838 (PREVIOUSLY PRESENTED). The process according to claim 837, wherein the lectin comprises concanavalin A.

Claim 839 (PREVIOUSLY PRESENTED). The process according to claim 837, wherein said lectin is conjugated to ferritin.

Claim 840 (PREVIOUSLY CANCELLED).

Claim 841 (PREVIOUSLY CANCELLED).

Claim 842 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a hormone.

Claim 843 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a metal-containing component.

Claim 844 (PREVIOUSLY PRESENTED). The process according to claim 843, wherein said metal-containing component is catalytic.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 61 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 845 (CURRENTLY AMENDED). The process according to claim 753, wherein said A comprises ~~an~~ a non-radioactively detectable indicator molecule moiety.

Claim 846 (CURRENTLY AMENDED). The process according to claim 845, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 847 (CURRENTLY AMENDED). The process according to claim 846, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 848 (CURRENTLY AMENDED). The process according to claim 847, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 849 (CURRENTLY AMENDED). The process according to claim 848, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 850 (CURRENTLY AMENDED). The process according to claims 848 or 849, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 851 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a fluorescent component.

Claim 852 (PREVIOUSLY PRESENTED). The process according to claim 851, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 853 (PREVIOUSLY PRESENTED). The process according to claim 852, wherein said fluorescent component comprises fluorescein.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 62 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 854 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a chemiluminescent component.

Claim 855 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 856 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises an antibody component.

Claim 857 (PREVIOUSLY PRESENTED). The process according to claim 830, wherein A comprises a chelating component.

Claim 858 (CURRENTLY AMENDED). The process according to claim 845, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 859 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said detectable non-radioactively labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

Claim 860 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said separating or resolving step is carried out electrophoretically.

Claim 861 (PREVIOUSLY PRESENTED). The process according to claims 721, 752 or 753, wherein said detecting step is carried out directly.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 63 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 862 (CURRENTLY AMENDED). The process according to claim 861, wherein the labeled fragments comprise one or more non-radioactively detectable indicator moieties and said direct detection is carried out using ~~one or more~~ these indicator molecules moieties.

Claim 863 (CURRENTLY AMENDED). The process according to claim 862, wherein said ~~one or more~~ non-radioactively detectable indicator molecules moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides or nucleotide analogs.

Claim 864 (CURRENTLY AMENDED). The process according to claim 863, wherein said ~~fluorescent~~ fluorescently labeled nucleotides or nucleotide analogs comprise fluorescent DNA.

Claim 865 (PREVIOUSLY PRESENTED). The process according to claim 861, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

Claim 866 (CURRENTLY AMENDED). The process according to claim 865, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating ~~compound~~ structure, a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 867 (PREVIOUSLY CANCELLED).

Claim 868 (PREVIOUSLY PRESENTED). The process according to claims 721, 752 or 753, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 64 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 869 (PREVIOUSLY PRESENTED). The process according to claim 868, wherein in said detecting step the indirectly detectable signal is selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

Claim 870 (PREVIOUSLY CANCELLED).

Claim 871 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 872 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

Claim 873 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising the steps of :

providing or generating detectable non-radioactive ~~non-radioactively labeled~~ nucleic acid fragments that are non-radioactively labeled , each fragment comprising : (a) a sequence complementary to said nucleic acid of interest or to a portion thereof , ~~wherein each of said fragments comprises~~ and (b) one or more detectable non-radioactively modified or labeled nucleotides ~~or nucleotide analogs, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog , the phosphate moiety, the phosphate analog , the base moiety or the base analog thereof ;~~

**Enz-5(D8)(C2)**

detecting non-radioactively the detectable non-radioactive labeled nucleic acid fragments with a sequencing gel; and

determining the sequence of said nucleic acid of interest.

Claim 874 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein the nucleic acid sequence of interest is derived from an organism.

Claim 875 (PREVIOUSLY PRESENTED). The process according to claim 874, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 876 (PREVIOUSLY PRESENTED). The process according to claims 875 or 878, wherein said organism comprises a mammal.

Claim 877 (PREVIOUSLY PRESENTED). The process according to claim 876, wherein said mammal comprises a human being.

Claim 878 (PREVIOUSLY PRESENTED). The process according to claim 874, wherein said organism is living.

Claim 879 (PREVIOUSLY PRESENTED). The process according to claims 874 or 878, wherein said organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 880 (PREVIOUSLY PRESENTED). The process according to claim 879, wherein said organism comprises a eukaryote.

Claim 881 (PREVIOUSLY PRESENTED). The process according to claim 880, wherein said eukaryotic nucleic acid sequence of interest is contained within a chromosome.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 66 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 882 (PREVIOUSLY PRESENTED). The process according to claim 880, wherein said eukaryote comprises a mammal.

Claim 883 (PREVIOUSLY PRESENTED). The process according to claim 882, wherein said mammalian nucleic acid sequence of interest is contained within a chromosome.

Claim 884 (PREVIOUSLY PRESENTED). The process according to claim 882, wherein said mammal comprises a human being.

Claim 885 (PREVIOUSLY PRESENTED). The process according to claim 884, wherein said human nucleic acid sequence of interest is contained within a chromosome.

Claim 886 (PREVIOUSLY PRESENTED). The process according to claim 885, wherein said human chromosomal nucleic acid sequence of interest is part of a human gene library.

Claim 887 (CURRENTLY AMENDED). The process according to claim 873, wherein in said providing or generating step the fragments are provided or generated by one or more primers, nucleoside triphosphates ~~or analogs thereof~~, or a combination thereof.

Claim 888 (CURRENTLY AMENDED). The process according to claim 887, wherein said nucleoside triphosphates are selected from the group consisting of ribonucleoside triphosphates, deoxyribonucleoside triphosphates, and dideoxyribonucleoside triphosphates, and ~~analog~~ a combination of any of the foregoing.

Claim 889 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein said fragments have been obtained or generated by a nucleic acid sequencing step or technique.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 67 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 890 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented and separated prior to detecting in said sequencing gel.

Claim 891. (CURRENTLY AMENDED). The process according to claim 873, wherein in said providing or generating step, the one or more ~~non-radioactive~~ modified or labeled nucleotides ~~or nucleotide analogs~~ have been incorporated into said nucleic acid fragment or fragments.

Claim 892 (CURRENTLY AMENDED). The process according to claim 891, wherein at least one of said ~~non-radioactive~~ modified or labeled nucleotides ~~or nucleotide analogs~~ is at a terminus of said fragment or fragments.

Claim 893 (PREVIOUSLY PRESENTED). The process according to claim 892, wherein said terminus comprises the 5' or the 3' terminus.

Claim 894 (PREVIOUSLY PRESENTED). The process according to claim 891, wherein said incorporation has been carried out in the presence of a primer.

Claim 895 (CURRENTLY AMENDED). The process according to claim 873, wherein said modified or labeled nucleotide ~~analog~~ can be attached terminally to DNA or RNA by means of an enzyme.

Claim 896. (PREVIOUSLY PRESENTED). The process according to claim 895, wherein said enzyme comprises terminal transferase.

Claim 897 (CURRENTLY AMENDED). The process according to claim 873, wherein said nucleotide ~~analog~~ can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 68 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 898 (PREVIOUSLY PRESENTED). The process according to claim 897, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 899 (PREVIOUSLY PRESENTED). The process according to claim 898, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.

Claim 900 (PREVIOUSLY CANCELLED).

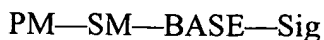
Claim 901 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 902 (CURRENTLY AMENDED). The process according to claim 901, wherein said polymerizing enzyme comprises a polymerase and the modified or labeled nucleotide is incorporated at a 3' terminus.

Claim 903 (PREVIOUSLY PRESENTED). The process according to claim 902, wherein said polymerizing enzyme is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 904 (CURRENTLY AMENDED). The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides ~~or nucleotide analogs~~ comprise one or more ~~members~~ nucleotide structures selected from the group consisting of one or more of :

- (i) a nucleotide structure ~~or nucleotide analog~~ having the formula



**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 69 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety  
~~or a base analog of any of the foregoing~~; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

(ii) a nucleotide structure ~~or nucleotide analog~~ having the formula

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide structure ~~or nucleotide analog~~, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

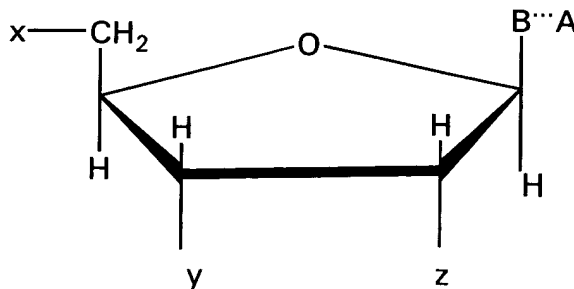
BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

Claim 905 (CURRENTLY AMENDED). The process according to claim 873, wherein in said providing or generating step, the ~~non-radioactive~~ modified or labeled nucleotides ~~or nucleotide analogs~~ have the structure:

(i)



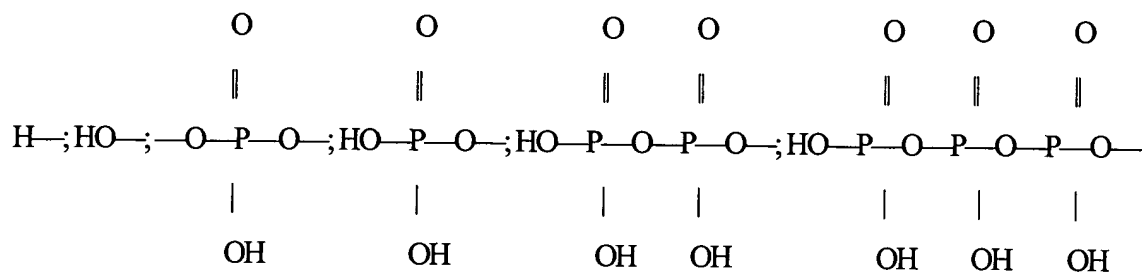
wherein B represents a purine moiety, a 7-deazapurine moiety, or a pyrimidine moiety ~~or an analog of any of the foregoing~~, and B is covalently bonded to the C1'-position of the ~~sugar~~ furanose-moiety ~~or sugar analog~~, provided that whenever B is a purine, ~~a purine analog~~, or a 7-deazapurine moiety ~~or a 7-deazapurine analog~~, the ~~sugar~~ furanose-moiety ~~or sugar analog~~ is attached at the N9 position of the purine moiety, ~~the purine analog~~, or of the 7-deazapurine moiety ~~or the 7-deazapurine analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the ~~sugar~~ furanose-moiety ~~or sugar analog~~ is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

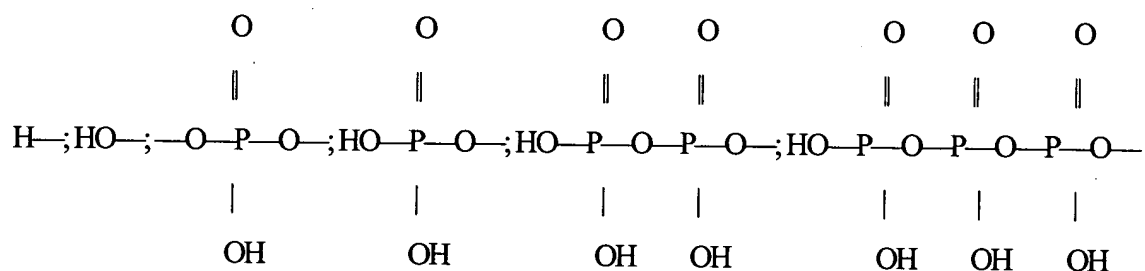
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine ~~or a purine analog~~, A is attached to the 8-position of the purine ~~or purine analog~~, if B is a 7-deazapurine ~~or 7-deazapurine analog~~, A is attached to the 7-position of the deazapurine ~~or deazapurine analog~~, and if B is a pyrimidine ~~or a pyrimidine analog~~, A is attached to the 5-position of the pyrimidine ~~or pyrimidine analog~~; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H— and HO—.

Claim 906 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein y and z are H—.

Claim 907 (CURRENTLY AMENDED). The process according to claim 873, wherein said PM ~~phosphate moiety or phosphate analog~~ is selected from the group consisting of a mono-phosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 908 (CURRENTLY AMENDED). The process according to claim 904, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide structure (i), (ii) or (iii) comprises a nucleoside mono-, di- or tri-phosphate.

Claim 909 (CURRENTLY AMENDED). The process according to claim 904, wherein said ~~sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Claim 910 (CURRENTLY CANCELLED). The process according to claim 909, wherein said monosaccharide comprises a furanose.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 73 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 911 (CURRENTLY AMENDED). The process according to claim ~~910~~ 904 , wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 912 (CURRENTLY AMENDED). The process according to claim 904, wherein ~~said base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 913 (CURRENTLY CANCELLED). The process according to claim 904, wherein said sugar moiety or sugar analog comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

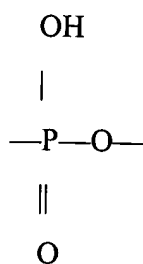
Claim 914 (CURRENTLY AMENDED). The process according to claim 904, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide structure (i) is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position when BASE is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 915 (CURRENTLY AMENDED). The process according to claim 904, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

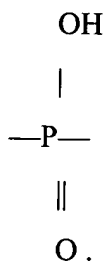
Claim 916 (CURRENTLY AMENDED). The process according to claim 910, wherein in said nucleotide structure (ii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 917 (CURRENTLY AMENDED). The process according to claim 910, wherein in said nucleotide structure (iii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 918 (CURRENTLY AMENDED). The process according to claim 904, wherein said covalent attachment in nucleotide structure ~~or nucleotide analog~~ (iii) is selected from the group consisting of



and



Claim 919 (CURRENTLY AMENDED). The process according to claim 904, wherein PM is a mono-, di- or tri-phosphate, and wherein in said nucleotide structure ~~or nucleotide analog~~ (iii), ~~the Sig moiety~~ is covalently attached to PM through a phosphorus or phosphate oxygen.

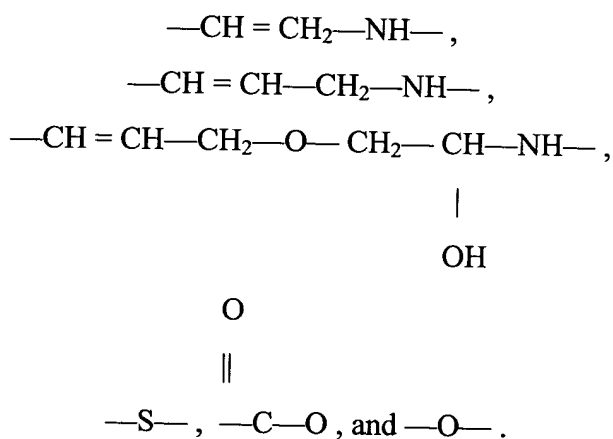
Claim 920 (CURRENTLY AMENDED). The process according to claim 904, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 921 (CURRENTLY AMENDED). The process according to claim 904, wherein in nucleotide structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide structure (i) , a —CH<sub>2</sub>NH— moiety, or both.



Claim 922 (CURRENTLY AMENDED). The process according to claim 904, wherein , in nucleotide structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 923 (CURRENTLY AMENDED). The process according to claim 904, wherein , in nucleotide structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide structure (i) , or any of the moieties



Claim 924 (CURRENTLY AMENDED). The process according to claim 904, wherein , in nucleotide structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Claim 925 (CURRENTLY AMENDED). The process according to claim 904, wherein in any of said ~~nucleotides~~ nucleotide structure (i), (ii) or (iii) said Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 926 (CURRENTLY AMENDED). The process according to claim 925, wherein , in nucleotide structure (i), said linkage group contains an amine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 77 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 927 (PREVIOUSLY PRESENTED). The process according to claim 926, wherein said amine comprises a primary amine.

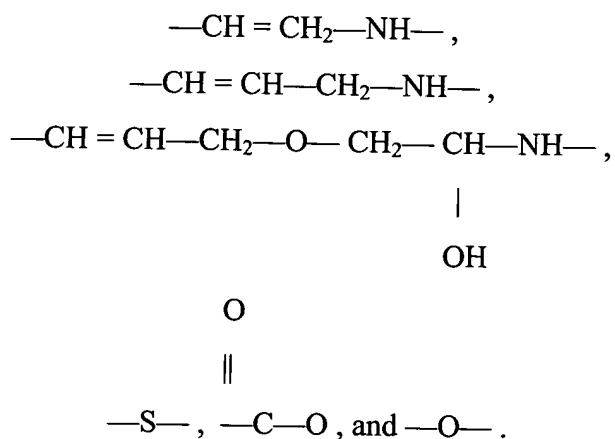
Claim 928 (PREVIOUSLY PRESENTED). The process according to claim 925, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 929 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein said covalent attachment does not interfere substantially with the characteristic ability of A to form a detectable non-radioactive signal.

Claim 930 (CURRENTLY AMENDED). The process according to claim 905, wherein said covalent attachment comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 931 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein said covalent attachment comprises an allylamine group.

Claim 932 (CURRENTLY AMENDED). The process according to claim 905, wherein said covalent attachment comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide structure (i) , or any of the moieties



Claim 933 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein said covalent attachment includes a glycosidic linkage moiety.

Claim 934 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein said A is covalently attached to B through a linkage group.

Claim 935 (CURRENTLY AMENDED). The process according to claim 934, wherein , in nucleotide structure (i), said linkage group contains an amine.

Claim 936 (PREVIOUSLY PRESENTED). The process according to claim 935, wherein said amine comprises a primary amine.

Claim 937 (PREVIOUSLY PRESENTED). The process according to claim 934, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 79 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 938 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein Sig comprises at least three carbon atoms.

Claim 939 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 940 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 941 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic moiety comprising at least five carbon atoms.

Claim 942 (PREVIOUSLY PRESENTED). The process according to claim 941, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 943 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 944 (PREVIOUSLY PRESENTED). The process according to claim 943, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 945 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 80 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 946 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 947 (PREVIOUSLY PRESENTED). The process according to claim 946, wherein Sig comprises an electron dense component.

Claim 948 (PREVIOUSLY CANCELLED).

Claim 949 (PREVIOUSLY PRESENTED). The process according to claim 946, wherein Sig comprises a magnetic component.

Claim 950 (PREVIOUSLY PRESENTED). The process according to claim 949, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 951 (PREVIOUSLY CANCELLED).

Claim 952 (PREVIOUSLY PRESENTED). The process according to claim 904, wherein Sig comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 953 (PREVIOUSLY PRESENTED). The process according to claim 952, wherein the binding protein comprises a lectin.

Claim 954 (PREVIOUSLY PRESENTED). The process according to claim 953, wherein the lectin comprises concanavalin A.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 81 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 955 (PREVIOUSLY PRESENTED). The process according to claim 953, wherein said lectin is conjugated to ferritin.

Claim 956 (PREVIOUSLY CANCELLED).

Claim 957 (PREVIOUSLY CANCELLED).

Claim 958 (PREVIOUSLY PRESENTED). The process according to claim 946, wherein Sig comprises a hormone.

Claim 959 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises a metal-containing component.

Claim 960 (PREVIOUSLY PRESENTED) The process according to claim 959, wherein said metal-containing component is catalytic.

Claim 961 (CURRENTLY AMENDED). The process according to claim 904, wherein said Sig ~~detectable non-radioactive moiety~~ comprises an a non-radioactively detectable indicator molecule moiety.

Claim 962 (CURRENTLY AMENDED). The process according to claim 961, wherein said indicator ~~molecule moiety~~ comprises an aromatic compound structure.

Claim 963 (CURRENTLY AMENDED). The process according to claim 962, wherein said aromatic ~~compound structure~~ is heterocyclic.

Claim 964 (CURRENTLY AMENDED). The process according to claim 963, wherein said heterocyclic aromatic ~~compound structure~~ is fluorescent.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 82 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 965 (CURRENTLY AMENDED). The process according to claim 904, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 966 (CURRENTLY AMENDED). The process according to claim 965, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 967 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises a fluorescent component.

Claim 968 (PREVIOUSLY PRESENTED) The process according to claim 967, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 969 (PREVIOUSLY PRESENTED) The process according to claim 968, wherein said fluorescent component comprises fluorescein.

Claim 970 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises a chemiluminescent component.

Claim 971 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 972 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises an antibody component.

Claim 973 (PREVIOUSLY PRESENTED) The process according to claim 946, wherein Sig comprises a chelating component.

**Enz-5(D8)(C2)**

Claim 974 (CURRENTLY AMENDED). The process according to claim 961, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 975 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 976 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 977 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 978 (PREVIOUSLY PRESENTED) The process according to claim 977, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 979 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 980 (PREVIOUSLY PRESENTED) The process according to claim 979, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 981 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises a monosaccharide, polysaccharide or an oligosaccharide.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 84 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 982 (PREVIOUSLY PRESENTED) The process according to claim 905, wherein A comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 983 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises an electron dense component.

Claim 984 (PREVIOUSLY CANCELLED).

Claim 985 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a magnetic component.

Claim 986 (PREVIOUSLY PRESENTED). The process according to claim 985, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 987 (PREVIOUSLY CANCELLED).

Claim 988 (PREVIOUSLY PRESENTED). The process according to claim 905, wherein A comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 989 (PREVIOUSLY PRESENTED). The process according to claim 988, wherein the binding protein comprises a lectin.

Claim 990 (PREVIOUSLY PRESENTED). The process according to claim 989, wherein the lectin comprises concanavalin A.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 85 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 991 (PREVIOUSLY PRESENTED). The process according to claim 989, wherein said lectin is conjugated to ferritin.

Claim 992 (PREVIOUSLY CANCELLED).

Claim 993 (PREVIOUSLY CANCELLED).

Claim 994 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a hormone.

Claim 995 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a metal-containing component.

Claim 996 (PREVIOUSLY PRESENTED). The process according to claim 995, wherein said metal-containing component is catalytic.

Claim 997 (CURRENTLY AMENDED). The process according to claim 905, wherein said A comprises ~~an~~ a non-radioactively detectable indicator ~~molecule~~ moiety.

Claim 998 (CURRENTLY AMENDED). The process according to claim 997, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 999 (CURRENTLY AMENDED). The process according to claim 998, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1000 (CURRENTLY AMENDED). The process according to claim 999, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 86 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1001 (CURRENTLY AMENDED). The process according to claim 1000, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 1002 (CURRENTLY AMENDED). The process according to claims 1000 or 1001, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1003 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a fluorescent component.

Claim 1004 (PREVIOUSLY PRESENTED). The process according to claim 1003, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1005 (PREVIOUSLY PRESENTED). The process according to claim 1004, wherein said fluorescent component comprises fluorescein.

Claim 1006 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a chemiluminescent component.

Claim 1007 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises an antigenic or hapten component capable of completing with an antibody specific to the component.

Claim 1008 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises an antibody component.

Claim 1009 (PREVIOUSLY PRESENTED). The process according to claim 982, wherein A comprises a chelating component.

**Enz-5(D8)(C2)**

Claim 1010 (CURRENTLY AMENDED). The process according to claim 1009, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent moiety component, a chromogenic moiety component, a chemiluminescent moiety component, a chelating moiety component, and a combination of any of the foregoing.

Claim 1011 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein said detectable non-radioactive labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

Claim 1012 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

Claim 1013 (PREVIOUSLY PRESENTED). The process according to claims 873, 904 or 905, wherein said detecting step is carried out directly.

Claim 1014 (CURRENTLY AMENDED). The process according to claim 1013, wherein the labeled fragments comprise one or more non-radioactively detectable indicator moieties and said direct detection is carried out using one or more of these indicator ~~molecules~~ moieties.

Claim 1015 (CURRENTLY AMENDED). The process according to claim 1014, wherein said one or more non-radioactively detectable indicator molecules moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~.

Claim 1016 (CURRENTLY AMENDED). The process according to claim 1015, wherein said ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 88 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1017 (CURRENTLY AMENDED). The process according to claim 1016, wherein said detecting step is carried out by means of a directly detectable signal provided by said ~~one or more~~ A, Sig or non-radioactive modified or labeled nucleotides ~~or nucleotide analogs~~, said A or said ~~Sig detectable non-radioactive moiety~~.

Claim 1018 (CURRENTLY AMENDED). The process according to claim 1013, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating ~~compound~~ structure, a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 1019 (PREVIOUSLY CANCELLED).

Claim 1020 (CURRENTLY AMENDED). The process according to claims 873, 904 or 905, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said ~~one or more non-radioactive~~ A, Sig or modified or labeled nucleotides ~~or nucleotide analogs~~, said A or said ~~Sig detectable non-radioactive moiety~~.

Claim 1021 (PREVIOUSLY PRESENTED). The process according to claim 1020, wherein said detecting step the indirectly detectable signal is selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

Claim 1022 (PREVIOUSLY CANCELLED).

Claim 1023 (CURRENTLY AMENDED). The process according to claim 873, wherein said ~~one or more non-radioactive~~ modified or labeled nucleotides ~~or nucleotide analogs~~ are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 89 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1024 (CURRENTLY AMENDED). The process according to claim 873, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said ~~one or more non-radioactive~~ modified or labeled nucleotides ~~or nucleotide analogs~~.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 90 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1025 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising ~~the step of~~ detecting non-radioactively with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments, wherein each of said fragments comprises: (a) comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises and (b) one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, provided that said modified or labeled nucleotide analogs can be enzymatically incorporated within, or onto a terminus of, said fragments which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar furanose moiety, the sugar analog, the phosphate moiety, the phosphate analog, or the base moiety or the base analog thereof.

Claim 1026 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein the nucleic acid sequence of interest is derived from an organism.

Claim 1027 (PREVIOUSLY PRESENTED). The process according to claim 1026, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 1028 (PREVIOUSLY PRESENTED). The process according to claim 1027, wherein said organism comprises a mammal.

Claim 1029 (PREVIOUSLY PRESENTED). The process according to claim 1028, wherein said mammal comprises a human being.

Claim 1030 (PREVIOUSLY PRESENTED). The process according to claim 1026, wherein said organism is living.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 91 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1031 (PREVIOUSLY PRESENTED). The process according to claims 1026 or 1030, wherein said organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 1032 (PREVIOUSLY PRESENTED). The process according to claim 1031, wherein said organism comprises a eukaryote.

Claim 1033 (PREVIOUSLY PRESENTED). The process according to claim 1032, wherein said eukaryotic nucleic acid sequence of interest is contained within a chromosome.

Claim 1034 (PREVIOUSLY PRESENTED). The process according to claim 1032, wherein said eukaryote comprises a mammal.

Claim 1035 (PREVIOUSLY PRESENTED). The process according to claim 1034, wherein said mammalian nucleic acid sequence of interest is contained within a chromosome.

Claim 1036 (PREVIOUSLY PRESENTED). The process according to claim 1034, wherein said mammal comprises a human being.

Claim 1037 (PREVIOUSLY PRESENTED). The process according to claim 1036, wherein said human nucleic acid sequence of interest is contained within a chromosome.

Claim 1038 (PREVIOUSLY PRESENTED). The process according to claim 1037, wherein said human chromosomal nucleic acid sequence of interest is part of a human gene library.

Claim 1039 (CURRENTLY AMENDED). The process according to claim 1025, wherein prior to said detecting step the fragments are provided or generated by one or more primers ; or nucleoside triphosphates ~~or analogs thereof~~ , or a combination thereof.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 92 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1040 (CURRENTLY AMENDED). The process according to claim 1039, wherein said nucleoside triphosphates are selected from the group consisting of ribonucleoside triphosphates, deoxyribonucleoside triphosphates, dideoxyribonucleoside triphosphates, and ~~analog~~s a combination of any of the foregoing.

Claim 1041 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said fragments have been obtained or generated by a nucleic acid sequencing step or technique.

Claim 1042 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

Claim 1043 (CURRENTLY AMENDED). The process according to claim 1025, wherein prior to said detecting step, the ~~one or more non-radioactive~~ modified or labeled nucleotides or nucleotide analogs have been incorporated into said ~~nucleic acid fragment or fragments~~.

Claim 1044 (CURRENTLY AMENDED). The process according to claim 1043, wherein at least one of said ~~non-radioactive~~ modified or labeled nucleotides or nucleotide analogs is at a terminus of said ~~fragment or fragments~~.

Claim 1045 (PREVIOUSLY PRESENTED). The process according to claim 1044, wherein said terminus comprises the 5' or the 3' terminus.

Claim 1046 (PREVIOUSLY PRESENTED). The process according to claim 1043, wherein said incorporation has been carried out in the presence of a primer.

Claim 1047 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said nucleotide analog can be attached terminally to DNA or RNA by means of an enzyme.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 93 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1048 (PREVIOUSLY PRESENTED). The process according to claim 1047, wherein said enzyme comprises terminal transferase.

Claim 1049 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said nucleotide analog can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

Claim 1050 (CURRENTLY CANCELLED). The process according to claim 1049, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 1051 (CURRENTLY AMENDED). The process according to claim 1049, wherein said incorporation enzymatic coupling can be is carried out by an enzymatic coupling means selected from the group consisting of a DNA ligase and or RNA ligase.

Claim 1052 (PREVIOUSLY CANCELLED).

Claim 1053 (CURRENTLY AMENDED). The process according to claim 1025 ~~or 1052~~ , wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 1054 (CURRENTLY AMENDED). The process according to claim 1053, wherein said polymerizing enzyme comprises a polymerase and the terminus is a 3' terminus.

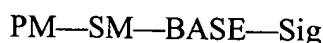
Claim 1055 (PREVIOUSLY PRESENTED). The process according to claim 1054, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 1056 (CURRENTLY AMENDED). The process according to claim 1025, wherein in said detecting step, the ~~non-radioactive~~ modified or labeled nucleotides or nucleotide analogs

**Enz-5(D8)(C2)**

comprise one or more nucleotide or nucleotide analog structures ~~members~~ selected from the group consisting of one or more of :

- (i) a nucleotide or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

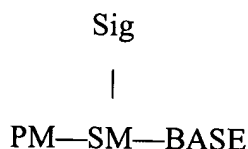
BASE is a pyrimidine, a purine or a 7-deazapurine base moiety

~~or a base analog of any of the foregoing~~; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

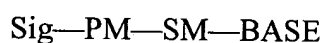
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide structure or nucleotide analog structure, ~~said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

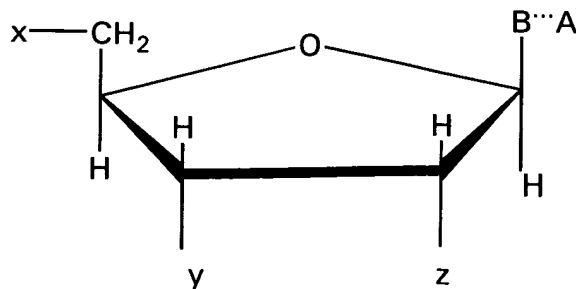
BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

Claim 1057 (CURRENTLY AMENDED). The process according to claim 1025, wherein prior to said detecting step, the ~~non-radioactive~~ modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



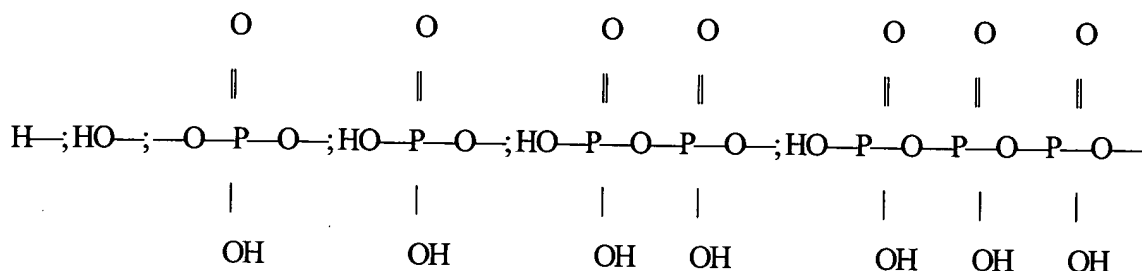
wherein B represents a purine moiety, a 7-deazapurine moiety, or a pyrimidine moiety, ~~or an analog of any of the foregoing~~, and B is covalently bonded to the C1'-position of the ~~sugar~~ furanose-moiety ~~or sugar analog~~, provided that whenever B is a purine, ~~a purine analog~~, or a 7-deazapurine moiety ~~or a 7-deazapurine analog~~, the ~~sugar~~ furanose-moiety ~~or sugar analog~~ is attached at the N9 position of the purine moiety, ~~the purine analog~~, or of the 7-deazapurine moiety ~~or the 7-deazapurine analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the ~~sugar~~ furanose-moiety ~~or sugar analog~~ is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

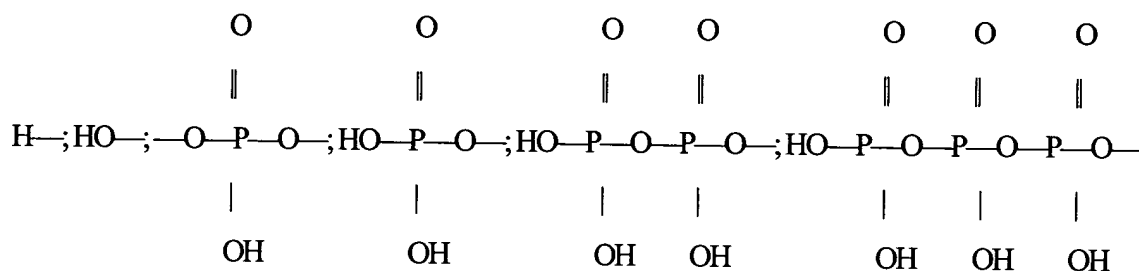
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine ~~or a purine analog~~, A is attached to the 8-position of the purine ~~or purine analog~~, if B is a 7-deazapurine ~~or 7-deazapurine analog~~, A is attached to the 7-position of the deazapurine ~~or deazapurine analog~~, and if B is a pyrimidine ~~or a pyrimidine analog~~, A is attached to the 5-position of the pyrimidine ~~or pyrimidine analog~~; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H— and HO—.

Claim 1058 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein y and z are H—.

Claim 1059 (CURRENTLY AMENDED). The process according to claim 1025, wherein ~~said~~ PM phosphate moiety or phosphate analog is selected from the group consisting of a mono-phosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 1060 (CURRENTLY AMENDED). The process according to claim 1056, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises a nucleoside mono-, di- or tri-phosphate.

Claim 1061 (CURRENTLY AMENDED). The process according to claims 1025 or 1056, wherein ~~said sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 98 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1062. (CURRENTLY CANCELLED) The process according to claim 1061, wherein said monosaccharide comprises a furanose.

Claim 1063 (CURRENTLY AMENDED). The process according to claim ~~1062~~ 1025 or 1056, wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 1064 (CURRENTLY AMENDED). The process according to claim 1056, wherein ~~said base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 1065 (CURRENTLY CANCELLED). The process according to claim 1056, wherein said sugar moiety or sugar analog comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

Claim 1066 (CURRENTLY AMENDED). The process according to claim 1056, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) ~~M~~ is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position when BASE is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 1067 (CURRENTLY AMENDED). The process according to claim 1056, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises

**Enz-5(D8)(C2)**

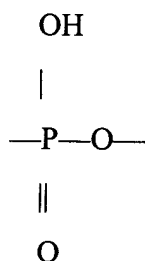
adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

Claim 1068 (CURRENTLY AMENDED). The process according to claim 1062, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said-furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said-furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

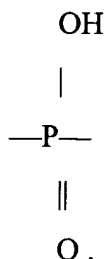
Claim 1069 (CURRENTLY AMENDED). The process according to claim 1062, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said-furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said-furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.



Claim 1070 (CURRENTLY AMENDED). The process according to claim 1056, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



and



Claim 1071 (CURRENTLY AMENDED). The process according to claim 1056, wherein PM is a mono-, di or tri-phosphate, and wherein said nucleotide or nucleotide analog structure (iii), the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

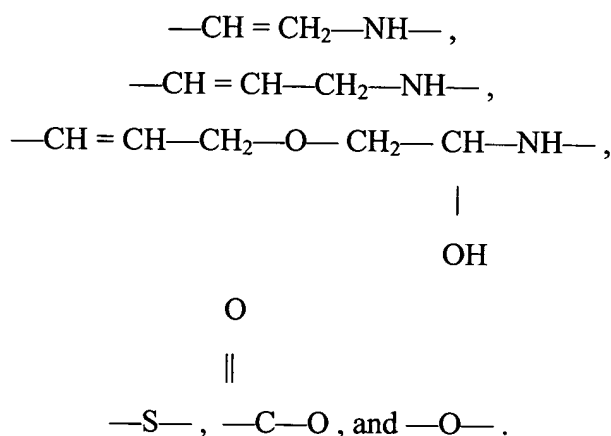
Claim 1072 (CURRENTLY AMENDED). The process according to claim 1056, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1073 (CURRENTLY AMENDED). The process according to claim 1056, wherein in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of: a —CH<sub>2</sub>NH— moiety, an

olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i), a  $\text{—CH}_2\text{NH—}$  moiety, or both.

Claim 1074 (CURRENTLY AMENDED). The process according to claim 1056, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 1075 (CURRENTLY AMENDED). The process according to claim 1056, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i), or any of the moieties



Claim 1076 (CURRENTLY AMENDED). The process according to claim 1056, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Claim 1077 (CURRENTLY AMENDED). The process according to claim 1056, wherein in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii), said Sig is covalently attached to BASE, SM or PM through a linkage group.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 102 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1078 (CURRENTLY AMENDED). The process according to claim 1077, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1079 (PREVIOUSLY PRESENTED). The process according to claim 1078, wherein said amine comprises a primary amine.

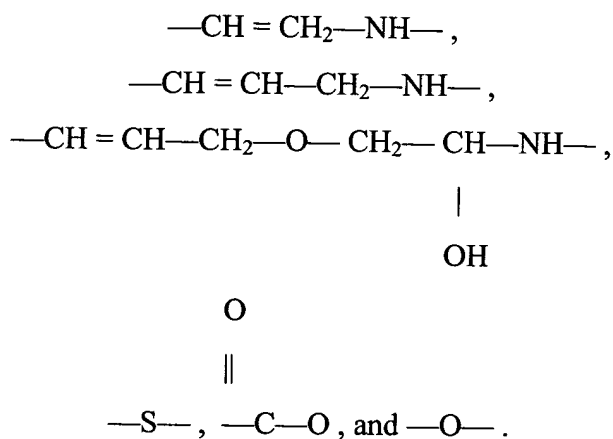
Claim 1080 (PREVIOUSLY PRESENTED). The process according to claim 1077, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1081 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein said covalent attachment does not interfere substantially with the characteristic ability of A to form a detectable non-radioactive signal.

Claim 1082 (CURRENTLY AMENDED). The process according to claim 1057, wherein said covalent attachment comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 1083 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein said covalent attachment comprises an allylamine group.

Claim 1084 (CURRENTLY AMENDED). The process according to claim 1057, wherein said covalent attachment comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 1085 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein said covalent attachment includes a glycosidic linkage moiety.

Claim 1086 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein said A is covalently attached to B through a linkage group.

Claim 1087 (PREVIOUSLY PRESENTED). The process according to claim 1086, wherein said linkage group contains an amine.

Claim 1088 (PREVIOUSLY PRESENTED). The process according to claim 1087, wherein said amine comprises a primary amine.

Claim 1089 (PREVIOUSLY PRESENTED). The process according to claim 1086, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 104 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1090 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein Sig comprises at least three carbon atoms.

Claim 1091 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1092 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1093 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic moiety comprising at least five carbon atoms.

Claim 1094 (PREVIOUSLY PRESENTED). The process according to claim 1093, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1095 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1096 (PREVIOUSLY PRESENTED). The process according to claim 1095, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 1097 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 105 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1098 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1099 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises an electron dense component.

Claim 1100 (PREVIOUSLY CANCELLED).

Claim 1101 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a magnetic component.

Claim 1102 (PREVIOUSLY PRESENTED). The process according to claim 1101, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1103 (PREVIOUSLY CANCELLED).

Claim 1104 (PREVIOUSLY PRESENTED). The process according to claim 1056, wherein Sig comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 1105 (PREVIOUSLY PRESENTED). The process according to claim 1104, wherein the binding protein comprises a lectin.

Claim 1106 (PREVIOUSLY PRESENTED). The process according to claim 1105, wherein the lectin comprises concanavalin A.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 106 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1107 (PREVIOUSLY PRESENTED). The process according to claim 1105, wherein said lectin is conjugated to ferritin.

Claim 1108 (PREVIOUSLY CANCELLED).

Claim 1109 (PREVIOUSLY CANCELLED).

Claim 1110 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a hormone.

Claim 1111 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a metal-containing component.

Claim 1112 (PREVIOUSLY PRESENTED). The process according to claim 1111, wherein said metal-containing component is catalytic.

Claim 1113 (CURRENTLY AMENDED). The process according to claim 1056, wherein said Sig ~~detectable non-radioactive moiety~~ comprises an a non-radioactively detectable indicator molecule moiety.

Claim 1114 (CURRENTLY AMENDED). The process according to claim 1113, wherein said indicator ~~molecule moiety~~ comprises an aromatic ~~compound~~ structure.

Claim 1115 (CURRENTLY AMENDED). The process according to claim 1114, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1116 (CURRENTLY AMENDED). The process according to claim 1115, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 107 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1117 (CURRENTLY AMENDED). The process according to claim 1116, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 1118 (CURRENTLY AMENDED). The process according to claim 1117, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1119 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a fluorescent component.

Claim 1120 (PREVIOUSLY PRESENTED). The process according to claim 1119, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1121 (PREVIOUSLY PRESENTED). The process according to claim 1120, wherein said fluorescent component comprises fluorescein.

Claim 1122 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a chemiluminescent component.

Claim 1123 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 1124 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises an antibody component.

Claim 1125 (PREVIOUSLY PRESENTED). The process according to claim 1098, wherein Sig comprises a chelating component.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 108 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1126 (CURRENTLY AMENDED). The process according to claim 1113, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 1127 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1128 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1129 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 1130 (PREVIOUSLY PRESENTED). The process according to claim 1129, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 1131 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1132 (PREVIOUSLY PRESENTED). The process according to claim 1131, wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent.

Claim 1133 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 1134 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 110 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1135 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises an electron dense component.

Claim 1136 (PREVIOUSLY CANCELLED).

Claim 1137 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises a magnetic component.

Claim 1138 (PREVIOUSLY PRESENTED). The process according to claim 1137, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1139 (PREVIOUSLY CANCELLED).

Claim 1140 (PREVIOUSLY PRESENTED). The process according to claim 1057, wherein A comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 1141 (PREVIOUSLY PRESENTED). The process according to claim 1140, wherein the binding protein comprises a lectin.

Claim 1142 (PREVIOUSLY PRESENTED). The process according to claim 1141, wherein the lectin comprises concanavalin A.

Claim 1143 (PREVIOUSLY PRESENTED). The process according to claim 1141, wherein said lectin is conjugated to ferritin.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 111 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1144 (PREVIOUSLY CANCELLED).

Claim 1145 (PREVIOUSLY CANCELLED).

Claim 1146 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises a hormone.

Claim 1147 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises a metal-containing component.

Claim 1148 (PREVIOUSLY PRESENTED). The process according to claim 1147, wherein said metal-containing component is catalytic.

Claim 1149 (CURRENTLY AMENDED). The process according to claim 1057, wherein said A comprises ~~an~~ a non-radioactively detectable indicator molecule moiety.

Claim 1150 (CURRENTLY AMENDED). The process according to claim 1149, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 1151 (CURRENTLY AMENDED). The process according to claim 1150, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1152 (CURRENTLY AMENDED). The process according to claim 1151, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1153 (CURRENTLY AMENDED). The process according to claim 1152, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 112 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1154 (CURRENTLY AMENDED). The process according to claims 1152 or 1153, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1155 (PREVIOUSLY PRESENTED). The process according to claim 1154, wherein A comprises a fluorescent component.

Claim 1156 (PREVIOUSLY PRESENTED). The process according to claim 1155, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1157 (PREVIOUSLY PRESENTED). The process according to claim 1156, wherein said fluorescent component comprises fluorescein.

Claim 1158 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises a chemiluminescent component.

Claim 1159 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises an antigenic or hapten component capable of completing with an antibody specific to the component.

Claim 1160 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises an antibody component.

Claim 1161 (PREVIOUSLY PRESENTED). The process according to claim 1134, wherein A comprises a chelating component.

Claim 1162 (CURRENTLY AMENDED). The process according to claim 1149, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 113 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

fluorescent component, a chromogenic component, a chemiluminescent component, a chelating component, and a combination of any of the foregoing.

Claim 1163 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said detectable labeled nucleic acid fragments are detectable non-radioactively by a fluorescent measurement, a chromogenic measurement, a chemiluminescent measurement, or a combination thereof.

Claim 1164 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

Claim 1165 (PREVIOUSLY PRESENTED). The process according to claims 1025, 1056 or 1057, wherein said detecting step is carried out directly.

Claim 1166 (CURRENTLY AMENDED). The process according to claim 1165, wherein the labeled fragments comprise one or more non-radioactively detectable indicator moieties and said direct detection is carried out using ~~one or more~~ these indicator molecules moieties.

Claim 1167 (CURRENTLY AMENDED). The process according to claim 1166, wherein said ~~one or more~~ non-radioactively detectable indicator molecules moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~.

Claim 1168 (CURRENTLY AMENDED). The process according to claim 1167, wherein said ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Claim 1169 (PREVIOUSLY PRESENTED). The process according to claim 1165, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 114 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

Claim 1170 (CURRENTLY AMENDED). The process according to claim 1165, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating ~~compound~~ structure, a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 1171 (PREVIOUSLY CANCELLED).

Claim 1172 (PREVIOUSLY PRESENTED). The process according to claims 1025, 1056 or 1057, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

Claim 1173 (PREVIOUSLY PRESENTED). The process according to claim 1172, wherein said detecting step the indirectly detectable signal is selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

Claim 1174 (PREVIOUSLY CANCELLED).

Claim 1175 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 115 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1176 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.



Claim 1177 (CURRENTLY AMENDED). A process for determining with a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid of interest or a portion thereof, said process comprising ~~the steps of~~ :

(A) providing

(i) (1) one or more nucleotides or nucleotide analogs that are: (a) detectable non-radioactive and (b) chemically modified or chemically labeled so as to be detectable nucleotides or nucleotide analogs, which provided that said nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid ; or

(ii) (2) one or more oligonucleotides or polynucleotides comprising at least one of said ~~detectable non-radioactive chemically modified or labeled nucleotide~~ nucleotides or nucleotide analog analog (1) ; or

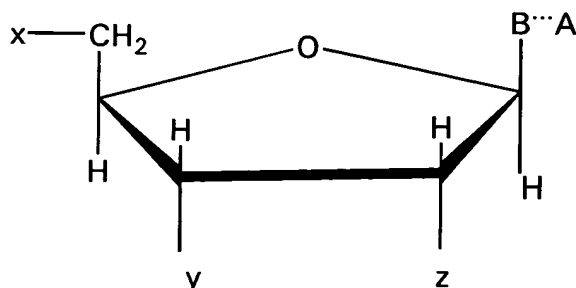
(iii) (3) both (i) and (ii) (1) and (2) ;

wherein said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (i) (1) and said oligonucleotides and polynucleotides (ii) (2) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, and wherein said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (1) have been non-radioactively modified or non-radioactively labeled , non-disruptively or disruptively , on at least one of the sugar furanose moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety ~~or the base analog thereof~~ ; and;

(B) incorporating said ~~one or more detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (i) (1) or said ~~one or more~~ oligonucleotides or polynucleotides (2) ~~comprising at least one chemically modified or labeled nucleotides or nucleotide analogs (ii)~~ , or both (i) and (ii) (1) and (2) , into or onto one or more of said nucleic acid fragments, ~~to prepare detectable non-radioactive labeled fragments~~, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof ~~and said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs~~ , and wherein said ~~detectable non-radioactive chemically modified or labeled~~

nucleotides or nucleotide analogs (1) comprise a nucleotide structure or nucleotide analog structure are selected from the group consisting of one or more of the following :

(i)

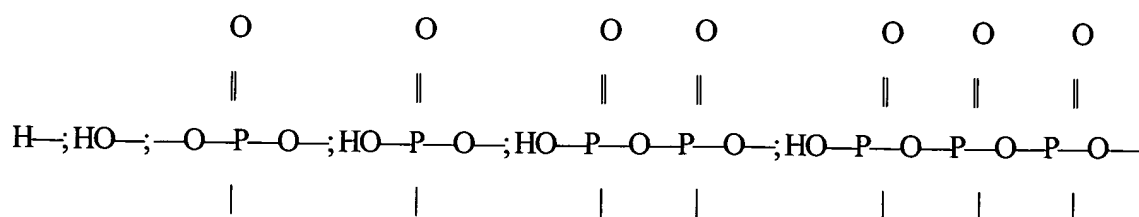


wherein B represents a purine moiety, a 7-deazapurine moiety, or a pyrimidine moiety, ~~or an analog of any of the foregoing~~, and B is covalently bonded to the C1-position of the sugar furanose-moiety or sugar analog, provided that whenever B is a purine moiety, ~~a purine analog~~, or a 7-deazapurine moiety ~~or a 7-deazapurine analog~~, the sugar furanose-moiety or sugar analog is attached at the N9 position of the purine moiety, ~~the purine analog~~, or of the 7-deazapurine moiety ~~or the 7-deazapurine analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the sugar furanose-moiety or sugar analog is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

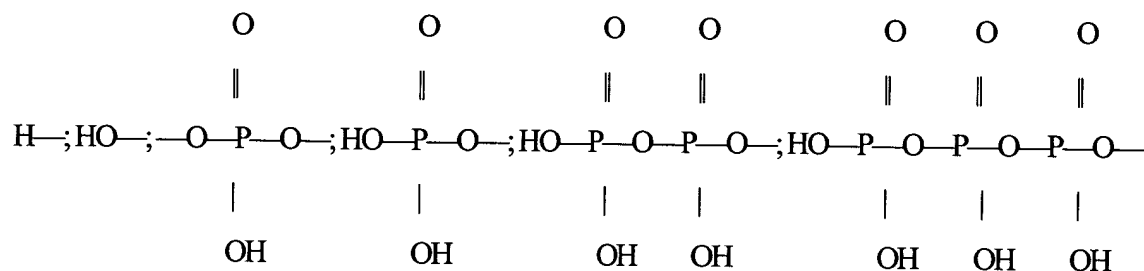
wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



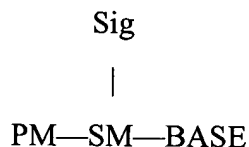


wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO-;

(ii)



wherein

PM is a phosphate moiety or phosphate analog,

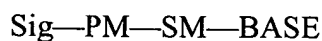
SM is a ~~sugar~~ furanose moiety or ~~sugar~~ analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said detectable non-radioactive labeled fragments to a sequencing gel;

(D) separating or resolving said detectable non-radioactive labeled fragments; and

(E) non-radioactively detecting directly or indirectly the presence of said detectable non-radioactive labeled fragments to determine the sequence of said nucleic acid of interest.

Claim 1178 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein the nucleic acid sequence of interest is derived from an organism.

Claim 1179 (PREVIOUSLY PRESENTED). The process according to claims 1178 or 1182, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 1180 (PREVIOUSLY PRESENTED). The process according to claim 1179, wherein said organism comprises a mammal.

Claim 1181 (PREVIOUSLY PRESENTED). The process according to claim 1180, wherein said mammal comprises a human being.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 120 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1182 (PREVIOUSLY PRESENTED). The process according to claim 1178, wherein said organism is living.

Claim 1183 (PREVIOUSLY PRESENTED). The process according to claims 1178 or 1182, wherein said organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 1184 (PREVIOUSLY PRESENTED). The process according to claim 1183, wherein said organism comprises a eukaryote.

Claim 1185 (PREVIOUSLY PRESENTED). The process according to claim 1184, wherein said eukaryotic nucleic acid sequence of interest is contained within a chromosome.

Claim 1186 (PREVIOUSLY PRESENTED). The process according to claim 1184, wherein said eukaryote comprises a mammal.

Claim 1187 (PREVIOUSLY PRESENTED). The process according to claim 1186, wherein said mammalian nucleic acid sequence of interest is contained within a chromosome.

Claim 1188 (PREVIOUSLY PRESENTED). The process according to claim 1186, wherein said mammal comprises a human being.

Claim 1189 (PREVIOUSLY PRESENTED). The process according to claim 1188, wherein said human nucleic acid sequence of interest is contained within a chromosome.

Claim 1190 (PREVIOUSLY PRESENTED). The process according to claim 1189, wherein said human chromosomal nucleic acid sequence of interest is part of a human gene library.

Claim 1191 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said incorporating step is carried out using an enzyme.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 121 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1192 (PREVIOUSLY PRESENTED). The process according to claim 1191, wherein said enzyme comprises a polymerase.

Claim 1193 (PREVIOUSLY PRESENTED). The process according to claim 1191, wherein said polymerase comprises DNA polymerase.

Claim 1194 (CURRENTLY AMENDED). The process according to claim 1177, wherein said ~~one or more chemically modified nucleotides or nucleotide analogs (1) or said other modified or unmodified nucleic acids~~ comprise a nucleoside di- or tri-phosphate.

Claim 1195 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said incorporating step is template dependent or template independent.

Claim 1196 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said incorporating step is template dependent.

Claim 1197 (CURRENTLY AMENDED). The process according to claim 1177, wherein the detectable labeled nucleic acid fragments prepared by said incorporating step comprises at least one internal modified nucleotide or nucleotide analog (1).

Claim 1198 (CURRENTLY AMENDED). The process according to claim 1177, wherein the detectable labeled nucleic acid fragments prepared by said incorporating step comprises at least one terminal modified nucleotide or nucleotide analog (1).

Claim 1199 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said nucleotide analog can be attached terminally to DNA or RNA by means of an enzyme.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 122 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1200 (PREVIOUSLY PRESENTED). The process according to claim 1199, wherein said enzyme comprises terminal transferase.

Claim 1201 (CURRENTLY CANCELLED). The process according to claim 1177, wherein said nucleotide analog can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

Claim 1202 (CURRENTLY CANCELLED). The process according to claim 1201, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 1203 (CURRENTLY CANCELLED). The process according to claim 1201, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.

Claim 1204 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said incorporation comprises nick translation.

Claim 1205 (CURRENTLY CANCELLED). The process according to claim 1177 or 1204, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 1206 (CURRENTLY CANCELLED). The process according to claim 1205, wherein said polymerizing enzyme comprises a polymerase.

Claim 1207 (CURRENTLY CANCELLED). The process according to claim 1206, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 123 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1208 (CURRENTLY AMENDED). The process according to claim 1177, wherein ~~said~~ PM phosphate moiety or phosphate analog is selected from the group consisting of a monophosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 1209 (CURRENTLY AMENDED). The process according to claim 1177, wherein any of ~~said nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprise a nucleoside mono-, di- or tri-phosphate.

Claim 1210 (CURRENTLY AMENDED). The process according to claim 1177, wherein ~~said~~ sugar moiety or sugar analog SM comprises a monosaccharide.

Claim 1211. (CURRENTLY CANCELLED) The process according to claim 1210, wherein ~~said~~ monosaccharide comprises a furanose.

Claim 1212 (CURRENTLY AMENDED). The process according to claim ~~1211~~ 1177, wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 1213 (CURRENTLY AMENDED). The process according to claim 1177, wherein ~~said~~ B in nucleotide or nucleotide analog structure (i) , ~~and or said BASE in nucleotides or nucleotide analogs~~ nucleotide or nucleotide analog structure (ii) or (iii) , is selected from the group consisting of a pyrimidine moiety ~~or pyrimidine analog~~ , a purine moiety ~~or purine analog~~ , a 7-deazapurine moiety ~~and a 7-deazapurine analog~~ , and a combination of any of the foregoing.

Claim 1214 (CURRENTLY AMENDED). The process according to claim 1177, wherein in ~~said chemically modified nucleotides~~ nucleotide or nucleotide analog structure (i) ; when B is a purine ~~or a purine analog~~ , A is attached to the 8-position of the purine moiety ~~or the purine analog~~ ; when B is a 7-deazapurine moiety ~~or a 7-deazapurine analog~~ , A is attached to the 7-position of the deazapurine moiety ~~or the 7-deazapurine analog~~ ; and when B is a pyrimidine

**Enz-5(D8)(C2)**



moiety ~~or a pyrimidine analog~~, A is attached to the 5-position of the pyrimidine moiety ~~or the pyrimidine analog~~.

Claim 1215 (CURRENTLY AMENDED). The process according to claim 1177, wherein in ~~said chemically modified nucleotides~~ nucleotide or nucleotide analog structure (i), A is covalently attached to ~~said~~ B at a position when B is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to B at a position when B is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 1216 (CURRENTLY AMENDED). The process according to claim 1177, wherein in ~~said chemically modified nucleotides~~ nucleotide or nucleotide analog structure (i) A is covalently attached to ~~said~~ B at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

Claim 1217 (CURRENTLY CANCELLED). The process according to claim 1177, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i) or (iii) or both is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

Claim 1218 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein at said incorporating step, A in the nucleotide or nucleotide analog structure (i) is covalently attached to B through a linkage group.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 125 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1219 (PREVIOUSLY PRESENTED). The process according to claim 1218, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1220 (CURRENTLY AMENDED). The process according to claim 1218, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1221 (PREVIOUSLY PRESENTED). The process according to claim 1220, wherein said amine comprises a primary amine.

Claim 1222 (CURRENTLY AMENDED). The process according to claim 1177, wherein said incorporating step, Sig in the nucleotide or nucleotide analog structure (ii) is covalently attached to SM through a linkage group.

Claim 1223 (PREVIOUSLY PRESENTED). The process according to claim 1222, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1224 (CURRENTLY AMENDED). The process according to claim 1222, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1225 (PREVIOUSLY PRESENTED). The process according to claim 1224, wherein said amine comprises a primary amine.

Claim 1226 (CURRENTLY AMENDED). The process according to claim 1177, wherein in said incorporating step, Sig in the nucleotide or nucleotide analog structure (iii) is covalently attached to PM through a linkage group.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 126 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1227 (PREVIOUSLY PRESENTED). The process according to claim 1226, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1228 (CURRENTLY AMENDED). The process according to claim 1226, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1229 (PREVIOUSLY PRESENTED). The process according to claim 1228, wherein said amine comprises a primary amine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

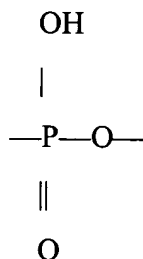
Filed: June 7, 1995

**Page 127 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

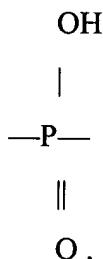
Claim 1230 (CURRENTLY AMENDED). The process according to claim 1211, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1231 (CURRENTLY AMENDED). The process according to claim 1211, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1232 (CURRENTLY AMENDED). The process according to claim 1177, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



and



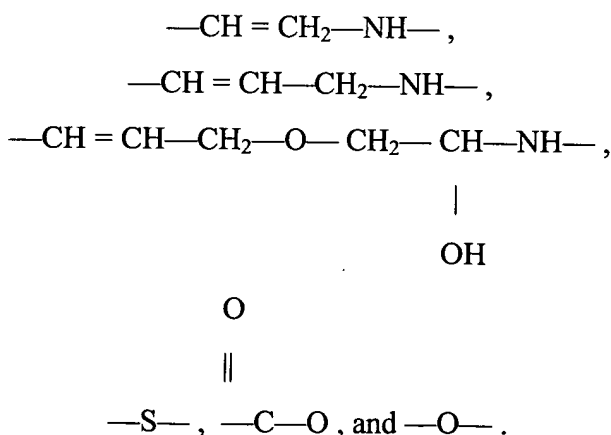
Claim 1233 (CURRENTLY AMENDED). The process according to claim 1177, wherein PM is a mono-, di- or tri-phosphate, and wherein in said nucleotide or nucleotide analog structure (iii), the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

Claim 1234 (CURRENTLY AMENDED). The process according to claim 1177, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of A or Sig to form a detectable non-radioactive signal.

1235 (CURRENTLY AMENDED). The process according to claim 1177, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of : a  $\text{—CH}_2\text{NH—}$  moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i), a  $\text{—CH}_2\text{NH—}$  moiety, or both.

Claim 1236 (CURRENTLY AMENDED). The process according to claim 1177, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 1237 (CURRENTLY AMENDED). The process according to claim 1177, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or any of the moieties



Claim 1238 (CURRENTLY AMENDED). The process according to claim 1177, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 130 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1239 (CURRENTLY AMENDED). The process according to claim 1177, wherein in said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), A is covalently attached to B through a linkage group, or in said ~~nucleotides or nucleotide analogs~~ nucleotide or nucleotide analog structure (ii) or (iii), Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 1240 (CURRENTLY AMENDED). The process according to claim 1239, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1241 (PREVIOUSLY PRESENTED). The process according to claim 1240, wherein said amine comprises a primary amine.

Claim 1242 (PREVIOUSLY PRESENTED). The process according to claim 1239, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1243 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig comprises at least three carbon atoms.

Claim 1244 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1245 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 131 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1246 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 1247 (PREVIOUSLY PRESENTED). The process according to claim 1141, wherein said A or Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1248 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 1249 (PREVIOUSLY PRESENTED). The process according to claim 1177, where said A or Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1250 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises an electron dense component.

Claim 1251 (PREVIOUSLY CANCELLED).

Claim 1252 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a magnetic component.

Claim 1253 (PREVIOUSLY PRESENTED). The process according to claim 1252, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1254 (PREVIOUSLY CANCELLED).

**Enz-5(D8)(C2)**



Claim 1255 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said A or Sig comprises a sugar residue and the sugar residue is capable of complexing with a sugar binding protein or a polysaccharide binding protein.

Claim 1256 (PREVIOUSLY PRESENTED). The process according to claim 1255, wherein the binding protein comprises a lectin.

Claim 1257 (PREVIOUSLY PRESENTED). The process according to claim 1256, wherein the lectin comprises concanavalin A.

Claim 1258 (PREVIOUSLY PRESENTED). The process according to claim 1256, wherein said lectin is conjugated to ferritin.

Claim 1259 (PREVIOUSLY CANCELLED).

Claim 1260 (PREVIOUSLY CANCELLED).

Claim 1261 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a hormone.

Claim 1262 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a metal-containing component.

Claim 1263 (PREVIOUSLY PRESENTED). The process according to claim 1262, wherein said metal-containing component is catalytic.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 133 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1264 (CURRENTLY AMENDED). The process according to claim 1177, wherein said A or Sig ~~detectable non-radioactive moiety~~ comprises an a non-radioactively detectable indicator ~~molecule moiety~~.

Claim 1265 (CURRENTLY AMENDED). The process according to claim 1264, wherein said indicator ~~molecule moiety~~ comprises an aromatic ~~compound~~ structure.

Claim 1266 (CURRENTLY AMENDED). The process according to claim 1265, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1267 (CURRENTLY AMENDED). The process according to claim 1266, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1268 (CURRENTLY AMENDED). The process according to claim 1267, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1269 (CURRENTLY AMENDED). The process according to claim 1268, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1270 (CURRENTLY AMENDED). The process according to claim 1264, wherein said indicator ~~molecule moiety~~ comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, and a chelating component, and a combination of any of the foregoing.

Claim 1271 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a fluorescent component.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 134 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1272 (PREVIOUSLY PRESENTED). The process according to claim 1271, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1273 (PREVIOUSLY PRESENTED). The process according to claim 1272, wherein said fluorescent component comprises fluorescein.

Claim 1274 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a chemiluminescent component.

Claim 1275 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises an antigenic or hapten component capable of completing with an antibody specific to the component.

Claim 1276 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises an antibody component.

Claim 1277 (PREVIOUSLY PRESENTED). The process according to claim 1249, wherein said A or Sig comprises a chelating component.

Claim 1278 (CURRENTLY AMENDED). The process according to claim 1177, wherein any of nucleotide or nucleotide ~~analog~~ analog structure (i), (ii) and (iii) ~~are~~ is detectable by a means selected from the group consisting of a fluorescent measurement and a chemiluminescent measurement, or a combination thereof.

Claim 1279 (CURRENTLY AMENDED). The process according to claim 1177, wherein ~~said~~ A or Sig is detectable when it is attached to the nucleotide or nucleotide analog structure (i), (ii) or (iii) directly or through a linkage group.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 135 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1280 (PREVIOUSLY PRESENTED). The process according to claim 1279, wherein said linkage group does not interfere substantially with the characteristic ability of A or Sig to form a detectable non-radioactive signal.

Claim 1281 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said detectable non-radioactive labeled nucleic acid fragment or fragments are terminally ligated or attached to a polypeptide.

Claim 1282 (PREVIOUSLY PRESENTED). The process according to claim 1281, wherein the polypeptide comprises a polylysine.

Claim 1283 (PREVIOUSLY PRESENTED). The process according to claim 1281, wherein the polypeptide comprises at least one member selected from the group consisting of avidin, streptavidin or anti-Sig immunoglobulin.

Claim 1284 (PREVIOUSLY PRESENTED). The process according to claim 1281, wherein said A or Sig comprises a ligand and the polypeptide comprises an antibody thereto.

Claim 1285 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said separating step is carried out electrophoretically.

Claim 1286 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said detecting step is carried out directly.

Claim 1287 (CURRENTLY AMENDED). The process according to claim 1286, wherein said direct detection is carried out on one or more non-radioactively detectable indicator ~~molecules~~ moieties.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 136 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1288 (CURRENTLY AMENDED). The process according to claim 1287, wherein said ~~one or more non-radioactively detectable~~ indicator ~~molecules~~ moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~.

Claim 1289 (CURRENTLY AMENDED). The process according to claim 1288, wherein said ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Claim 1290 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said detecting step is carried out by means of a directly detectable signal provided by said A or Sig detectable non-radioactive moiety.

Claim 1291 (CURRENTLY AMENDED). The process according to claim 1290, wherein said detecting step the directly detectable signal providing A or Sig detectable non-radioactive moiety comprises a member selected from the group consisting of a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 1292 (PREVIOUSLY PRESENTED). The process according to claim 1290, wherein said detecting step the directly detectable signal is provided by an enzyme.

Claim 1293 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said A or Sig detectable non-radioactive moiety.

Claim 1294 (PREVIOUSLY PRESENTED). The process according to claim 1293, wherein said detecting step the indirectly detectable signal is provided by a member selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 137 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1295 (PREVIOUSLY CANCELLED).

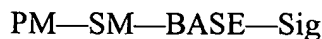
Claim 1296 (CURRENTLY AMENDED). The process according to claim 1293, wherein said detecting step the indirectly detectable signal providing Sig ~~detectable non-radioactive moiety~~ comprises a ~~compound~~ structure capable of binding to an insoluble phase.

Claim 1297 (PREVIOUSLY PRESENTED). The process according to claim 1177, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 1298 (CURRENTLY AMENDED). A process for detecting a nucleic acid of interest in a sample, which process comprises ~~the steps of~~ :

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more detectable non-radioactive labeled oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs ~~are~~ comprise a nucleotide structure or nucleotide analog structure selected from the group consisting of one or more of :

(i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

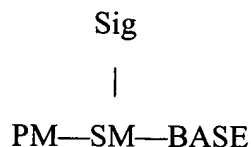
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

**Enz-5(D8)(C2)**

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety ~~or a base analog of any of the foregoing~~; and

Sig is a detectable non-radioactive moiety that comprises at least three carbon atoms , wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a ~~base moiety or base analog~~, and

Sig is a detectable non-radioactive moiety that comprises at least three carbon atoms , wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

- (iii) a nucleotide structure or nucleotide analog structure ~~, said nucleotide~~ having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety that comprises at least three carbon atoms , wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; provided that when said nucleotide or nucleotide analog structure (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting non-radioactively the presence of ~~said Sig detectable non-radioactive moieties~~ in any of the detectable non-radioactive labeled oligo- or polynucleotides which have hybridized to said nucleic acid of interest.

Claim 1299 (PREVIOUSLY PRESENTED). The process according to claim-1298, wherein the nucleic acid of interest comprises DNA, RNA or a DNA-RNA hybrid.

Claim 1300 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the nucleic acid of interest is double-stranded or single-stranded.

Claim 1301 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the nucleic acid of interest has been rendered single-stranded.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 140 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1302 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the nucleic acid of interest is derived from an organism.

Claim 1303 (PREVIOUSLY PRESENTED). The process according to claim 1302, wherein the organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 1304 (PREVIOUSLY PRESENTED). The process according to claims 1302 or 1305, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 1305 (PREVIOUSLY PRESENTED). The process according to claim 1302, wherein said organism is living.

Claim 1306 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the sample is suspected of containing an etiological agent and the nucleic acid of interest is naturally associated with the etiological agent.

Claim 1307 (PREVIOUSLY PRESENTED). The process according to claim 1306, wherein the sample is of human or animal origin and the etiological agent is selected from the group consisting of bacteria, virus and fungi.

Claim 1308 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said nucleic acid of interest is derived from a member selected from the group consisting of *Streptococcus pyrogenes*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, and any combinations of the foregoing.

Claim 1309 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said one or more oligo- or polynucleotides are derived from *Neisseria gonorrhoeae*.

**Enz-5(D8)(C2)**

Claim 1310 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the sample comprises a bacterium suspected of containing a nucleic acid of interest which imparts resistance to an antibiotic and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the sequence of the bacterium which confers resistance to the antibiotic.

Claim 1311 (PREVIOUSLY PRESENTED). The process according to claim 1310, wherein when said bacterium is *Streptococcus pyrogenes* or *Neisseria meningitidis*, said antibiotic is penicillin, wherein when said bacterium is *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Streptococcus pyrogenes*, or *Neisseria gonorrhoeae*, said antibiotic is a tetracycline, and wherein when said bacterium is *Mycobacterium tuberculosis*, said antibiotic is an aminoglycoside.

Claim 1312 (PREVIOUSLY PRESENTED). The process according to claim 1311, wherein said bacterium is *Neisseria gonorrhoeae* and said antibiotic is selected from the group consisting of penicillin, tetracycline, aminoglycoside and combinations thereof.

Claim 1313 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the sample is suspected of containing a nucleic acid of interest associated with a genetic disorder and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the nucleic acid associated with the genetic disorder.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 142 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1314 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the sample is suspected of containing a nucleic acid of interest associated with thalassemia and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the nucleic acid which is absent in the thalassemic subjects.

Claim 1315 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said process is utilized for chromosomal karyotyping which comprises contacting the sample with a series of the oligo- or polynucleotides which are complementary to a series of known genetic sequences located on chromosomes.

Claim 1316 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the sample is suspected of containing a nucleic acid which includes a terminal polynucleotide sequence poly A and wherein the oligo- or polynucleotide comprises a modified poly U molecule in which at least one uracil moiety has been modified by chemical addition of Sig to the 5' position of said uracil moiety.

Claim 1317 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said process is utilized to determine the number of copies of an individual chromosome in a sample.

Claim 1318 (CURRENTLY AMENDED). The process according to claim 1298, wherein said nucleotide or nucleotide analog structure (i), (ii) or (iii) can be attached terminally to DNA or RNA by means of an enzyme.

Claim 1319 (PREVIOUSLY PRESENTED). The process according to claim 1318, wherein said enzyme comprises terminal transferase.

Claim 1320 (CURRENTLY AMENDED). The process according to claim 1298, wherein said nucleotide or nucleotide analog structure (i), (ii) or (iii) can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

**Enz-5(D8)(C2)**

Claim 1321 (PREVIOUSLY PRESENTED). The process according to claim 1320, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 1322 (PREVIOUSLY PRESENTED). The process according to claim 1320, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.

Claim 1323 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said incorporation comprises nick translation.

Claim 1324 (PREVIOUSLY PRESENTED). The process according to claim 1298 or 1323, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 1325 (PREVIOUSLY PRESENTED). The process according to claim 1324, wherein said polymerizing enzyme comprises a polymerase.

Claim 1326 (PREVIOUSLY PRESENTED). The process according to claim 1325, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 1327 (CURRENTLY AMENDED). The process according to claim 1298, wherein ~~said~~ PM phosphate moiety or phosphate analog is selected from the group consisting of a monophosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.

Claim 1328 (CURRENTLY AMENDED). The process according to claim 1298, wherein any of ~~said nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) ~~comprise~~ comprises a nucleoside mono-, di- or tri-phosphate.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 144 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1329 (CURRENTLY AMENDED). The process according to claim 1298, wherein ~~said~~ ~~sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Claim 1330. (CURRENTLY CANCELLED) The process according to claim 1329, wherein said monosaccharide comprises a furanose.

Claim 1331 (CURRENTLY AMENDED). The process according to claim ~~1330~~ 1329 , wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 1332 (CURRENTLY AMENDED). The process according to claim 1298, wherein ~~said~~ ~~base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 1333 (CURRENTLY CANCELLED). The process according to claim 1298, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

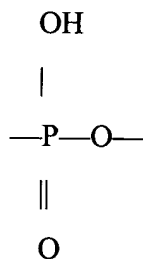
Claim 1334 (CURRENTLY AMENDED). The process according to claim 1298, wherein said modified or labeled nucleotides or nucleotide analogs comprise nucleotide or nucleotide analog structure (i) and said Sig detectable non-radioactive moiety in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, ~~or~~ and said Sig is covalently attached to BASE at a position when BASE is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 1335 (CURRENTLY AMENDED). The process according to claim 1298, wherein ~~said Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

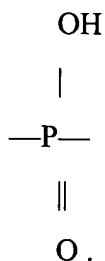
Claim 1336 (CURRENTLY AMENDED). The process according to claim 1333, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said monosaccharide or furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1337 (CURRENTLY AMENDED). The process according to claim 1333, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said monosaccharide or furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said monosaccharide or furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1338 (CURRENTLY AMENDED). The process according to claim 1298, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



and



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 147 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1339 (CURRENTLY AMENDED). The process according to claim 1298, wherein PM is a mono-, di or tri-phosphate, and wherein in said nucleotide or nucleotide analog structure (iii), ~~the Sig detectable non-radioactive moiety~~ is covalently attached to PM through a phosphorus or phosphate oxygen.

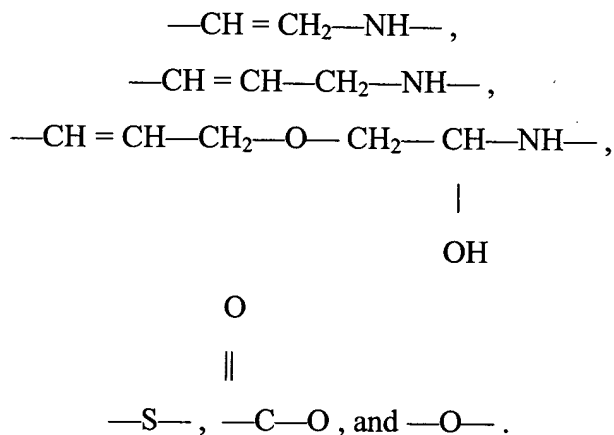
Claim 1340 (CURRENTLY AMENDED). The process according to claim 1298, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1341 (CURRENTLY AMENDED). The process according to claim 1298, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 1342 (CURRENTLY AMENDED). The process according to claim 1298, wherein , in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.



Claim 1343 (CURRENTLY AMENDED). The process according to claim 1298, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises or includes : an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , or any of the moieties



Claim 1344 (CURRENTLY AMENDED). The process according to claim 1298, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ includes a glycosidic linkage moiety.

Claim 1345 (CURRENTLY AMENDED). The process according to claim 1298, wherein in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) , said Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 1346 (CURRENTLY AMENDED). The process according to claim 1345, wherein, in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1347 (PREVIOUSLY PRESENTED). The process according to claim 1346, wherein said amine comprises a primary amine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 149 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1348 (PREVIOUSLY PRESENTED). The process according to claim 1345, wherein said linkage group does not substantially interfere with nucleic acid hybridization or double-stranded nucleic acid formation.

Claim 1349 (PREVIOUSLY PRESENTED). The process according to claim 1345, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1350 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig comprises at least three carbon atoms.

Claim 1351 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1352 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1353 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 1354 (PREVIOUSLY PRESENTED). The process according to claim 1353, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1355 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

**Enz-5(D8)(C2)**

Claim 1356 (PREVIOUSLY PRESENTED). The process according to claim 1355, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1357 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 1358 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1359 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises an electron dense component.

Claim 1360 (PREVIOUSLY PRESENTED). The process according to claim 1359, wherein said electron dense component comprises ferritin.

Claim 1361 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises a magnetic component.

Claim 1362 (PREVIOUSLY PRESENTED). The process according to claim 1361, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1363 (PREVIOUSLY PRESENTED). The process according to claim 1361, wherein said magnetic component comprises magnetic beads.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 151 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1364 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig comprises a sugar residue and the sugar residue is complexed with or attached to a sugar binding protein or a polysaccharide binding protein.

Claim 1365 (PREVIOUSLY PRESENTED). The process according to claim 1364, wherein the binding protein comprises a lectin.

Claim 1366 (PREVIOUSLY PRESENTED). The process according to claim 1365, wherein the lectin comprises concanavalin A.

Claim 1367 (PREVIOUSLY PRESENTED). The process according to claim 1365, wherein said lectin is conjugated to ferritin.

Claim 1368 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises an enzyme.

Claim 1369 (PREVIOUSLY PRESENTED). The process according to claim 1368, wherein said enzyme is selected from the group consisting of alkaline phosphatase, acid phosphatase,  $\beta$ -galactosidase, ribonuclease, glucose oxidase and peroxidase, or a combination thereof.

Claim 1370 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises a hormone.

Claim 1371 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises a metal-containing component.

Claim 1372 (PREVIOUSLY PRESENTED). The process according to claim 1371, wherein said metal-containing component is catalytic.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 152 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1373 (CURRENTLY AMENDED). The process according to claim 1298, wherein said ~~Sig detectable non-radioactive moiety~~ comprises ~~an~~ a non-radioactively detectable indicator ~~molecule moiety~~.

Claim 1374 (CURRENTLY AMENDED). The process according to claim 1373, wherein said indicator ~~molecule moiety~~ comprises an aromatic ~~compound~~ structure.

Claim 1375 (CURRENTLY AMENDED). The process according to claim 1374, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1376 (CURRENTLY AMENDED). The process according to claim 1375, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1377 (CURRENTLY AMENDED). The process according to claim 1376, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 1378 (CURRENTLY AMENDED). The process according to claim 1377, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1379 (CURRENTLY AMENDED). The process according to claim 1358, wherein Sig comprises a fluorescent component.

Claim 1380 (PREVIOUSLY PRESENTED). The process according to claim 1379, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1381 (PREVIOUSLY PRESENTED). The process according to claim 1380, wherein said fluorescent component comprises fluorescein.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 153 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1382 (PREVIOUSLY PRESENTED). The process according to claim 1358 wherein Sig comprises a chemiluminescent component.

Claim 1383 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises an antigenic or hapten component capable of complexing with an antibody specific to the component.

Claim 1384 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises an antibody component.

Claim 1385 (PREVIOUSLY PRESENTED). The process according to claim 1358, wherein Sig comprises a chelating component.

Claim 1386 (CURRENTLY AMENDED). The process according to claim 1373, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, and a chelating component, and a combination of any of the foregoing.

Claim 1387 (CURRENTLY AMENDED). The process according to claim 1298, wherein any of nucleotide or nucleotide analog structure ~~analog~~s (i), (ii) and (iii) are detectable by a means selected from the group consisting of a fluorescent measurement and a chemiluminescent measurement, or a combination thereof.

Claim 1388 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig is detectable non-radioactively when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

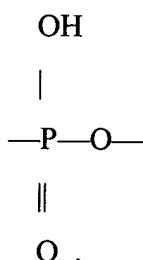
Filed: June 7, 1995

**Page 154 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1389 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein Sig is detectable non-radioactively when it is attached to the nucleotide directly or through a linkage group.

Claim 1390 (PREVIOUSLY PRESENTED). The process according to claim 1389, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1391 (CURRENTLY AMENDED). The process according to claim 1298, wherein Sig in said nucleotide or nucleotide analog structure (iii) is covalently attached to PM via the chemical linkage



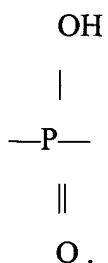
Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 155 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1392 (CURRENTLY AMENDED). The process according to claim 1298, wherein Sig in said nucleotide or nucleotide analog structure (iii) is covalently attached to PM via the chemical linkage



Claim 1393 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein the oligo- or polynucleotide is terminally ligated or attached to a polypeptide.

Claim 1394 (PREVIOUSLY PRESENTED). The process according to claim 1298, further comprising contacting the sample with a polypeptide capable of forming a complex with Sig and a moiety which can be detected when the complex is formed.

Claim 1395 (PREVIOUSLY PRESENTED). The process according to claims 1393 or 1394, wherein the polypeptide comprises a polylysine.

Claim 1396 (PREVIOUSLY PRESENTED). The process according to claims 1393 or 1394, wherein the polypeptide comprises at least one member selected from the group consisting of avidin, streptavidin or anti-Sig immunoglobulin.

Claim 1397 (PREVIOUSLY PRESENTED). The process according to claim 1394, wherein Sig comprises a ligand and the polypeptide comprises an antibody thereto.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 156 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1398 (PREVIOUSLY PRESENTED). The process according to claim 1394, wherein the moiety which can be detected when the complex is formed is selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1399 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said detecting step is carried out directly.

Claim 1400 (CURRENTLY AMENDED). The process according to claim 1399, wherein said direct detection is carried out ~~on one or more nucleotides or nucleotide analogs comprising by~~ non-radioactively detecting indicator molecules moieties on the modified or labeled nucleotides or nucleotide analogs.

Claim 1401 (CURRENTLY AMENDED). The process according to claim 1400, wherein said ~~one or more indicator molecules moieties~~ comprise fluorescent fluorescently labeled nucleotides ~~or nucleotide analogs.~~

Claim 1402 (CURRENTLY AMENDED). The process according to claim 1401, wherein said ~~fluorescent fluorescently labeled~~ nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Claim 1403 (CURRENTLY AMENDED). The process according to claim 1298, wherein said detecting step is carried out by means of a directly detectable non-radioactive signal provided by ~~said Sig detectable non-radioactive moiety.~~

Claim 1404 (CURRENTLY AMENDED). The process according to claim 1403, wherein said detecting step the directly detectable non-radioactive signal comprises a member selected from the group consisting of a fluorogenic ~~compound~~ structure, a phosphorescent ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 1405 (PREVIOUSLY PRESENTED). The process according to claim 1403, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

Claim 1406 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said detecting step is carried out by means of a indirectly detectable non-radioactive signal provided by said Sig detectable non-radioactive moiety.

Claim 1407 (PREVIOUSLY PRESENTED). The process according to claim 1406, wherein said detecting step the indirectly detectable non-radioactive signal is selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

Claim 1408 (PREVIOUSLY CANCELLED).

Claim 1409 (PREVIOUSLY PRESENTED). The process according to claim 1298, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 1410 (PREVIOUSLY PRESENTED). The process according to claim 1255, further comprising one or more washing steps.

Claim 1411 (CURRENTLY AMENDED). A process for detecting a nucleic acid of interest in a sample, which process comprises ~~the steps of~~ :

**Enz-5(D8)(C2)**

(A) providing:

(i) an oligo- or polynucleotide that comprises two segments, the first segment comprising a nucleotide sequence that is (1) complementary to and capable of specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof, and the second segment comprising an operator sequence that is (2) capable of binding to or complexing with a non-radioactively detectable protein; and

(ii) a non-radioactively detectable protein which is non-radioactive and has a binding affinity to a specific nucleic acid said operator sequence;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex; and

(C) detecting non-radioactively the presence of said non-radioactively detectable protein in said complex to detect said nucleic acid of interest.

Claim 1412 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the nucleic acid of interest comprises DNA, RNA or a DNA-RNA hybrid.

Claim 1413 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the nucleic acid of interest is double-stranded or single-stranded.

Claim 1414 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the nucleic acid of interest has been rendered single-stranded.

Claim 1415 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the nucleic acid of interest is derived from an organism.

Claim 1416 (PREVIOUSLY PRESENTED). The process according to claim 1415, wherein the living organism is selected from the group consisting of prokaryotes and eukaryotes.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 159 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1417 (PREVIOUSLY PRESENTED). The process according to claims 1415 or 1418, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 1418 (PREVIOUSLY PRESENTED). The process according to claim 1415, wherein said organism is living.

Claim 1419 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the sample is suspected of containing an etiological agent and the nucleic acid of interest is naturally associated with the etiological agent.

Claim 1420 (PREVIOUSLY PRESENTED). The process according to claim 1419, wherein the sample is of human or animal origin and the etiological agent is selected from the group consisting of bacteria, virus and fungi.

Claim 1421 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said nucleic acid of interest are derived from a member selected from the group consisting of *Streptococcus pyrogenes*, *Neisseria meningitides*, *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, and any combinations of the foregoing.

Claim 1422 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said one or more oligo- or polynucleotides are derived from *Neisseria gonorrhoeae*.

Claim 1423 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the sample comprises a bacterium suspected of containing a nucleic acid of interest which imparts resistance to an antibiotic and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the sequence of the bacterium which confers resistance to the antibiotic.

**Enz-5(D8)(C2)**

Claim 1424 (PREVIOUSLY PRESENTED). The process according to claim 1423, wherein when said bacterium is *Streptococcus pyrogenes* or *Neisseria meningitidis*, said antibiotic is penicillin, wherein when said bacterium is *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Streptococcus pyrogenes*, or *Neisseria gonorrhoea*, said antibiotic is a tetracycline, and wherein when said bacterium is *Mycobacterium tuberculosis*, said antibiotic is an aminoglycoside.

Claim 1425 (PREVIOUSLY PRESENTED). The process according to claim 1424, wherein said bacterium is *Neisseria gonorrhoeae* and said antibiotic is selected from the group consisting of penicillin, tetracycline, aminoglycoside and combinations thereof.

Claim 1426 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the sample is suspected of containing a nucleic acid of interest associated with a genetic disorder and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the nucleic acid associated with the genetic disorder.

Claim 1427 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein the sample is suspected of containing a nucleic acid of interest associated with thalassemia and wherein the oligo- or polynucleotide comprises a polynucleotide complementary to the nucleic acid which is absent in the thalassemic subjects.

Claim 1428 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said process is utilized for chromosomal karyotyping which comprises contacting the sample with a series of the oligo- or polynucleotides (i) which are complementary to a series of known genetic sequences located on chromosomes.

Claim 1429 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said process is utilized to determine the number of copies of an individual chromosome in a sample.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 161 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1430 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said non-radioactive detectable protein is selected from the group consisting of an antibody, a promoter, a repressor and an inducer.

Claim 1431 (PREVIOUSLY PRESENTED). The process according to claim 1430, wherein said repressor comprises a lac repressor.

Claim 1432 (PREVIOUSLY PRESENTED). The process according to claim 1430, wherein said at least one protein binding nucleic acid sequence is covalently attached to said oligo- or polynucleotide.

Claim 1433 (PREVIOUSLY PRESENTED). The process according to claim 1432, wherein said covalent attachment comprises ligation.

Claim 1434 (PREVIOUSLY PRESENTED). The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to bind to any hybrid formed between said oligo- or polynucleotide and said nucleic acid of interest.

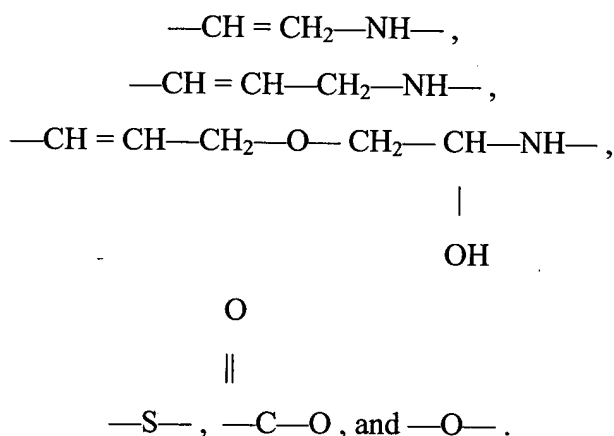
Claim 1435 (PREVIOUSLY PRESENTED). The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to be detected non-radioactively when bound to any hybrid formed between said oligo- or polynucleotide and said nucleic acid of interest.

Claim 1436 (CURRENTLY AMENDED). The process according to claim 1432, wherein in nucleotide or nucleotide analog structure (i), said covalent attachment comprises a member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to ~~the~~ nucleotide or nucleotide analog structure (i) , a  $\text{CH}_2\text{NH}$ — moiety, or both.

**Enz-5(D8)(C2)**

Claim 1437 (CURRENTLY AMENDED). The process according to claim 1436, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment comprises an allylamine group.

Claim 1438 (CURRENTLY AMENDED). The process according to claim 1436, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment comprises or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or any of the moieties



Claim 1439 (CURRENTLY AMENDED). The process according to claim 1432, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment includes a glycosidic linkage moiety.

Claim 1440 (CURRENTLY AMENDED). The process according to claim 1432, wherein said protein binding sequence is covalently attached to any of the base, phosphate, or ~~sugar~~ furanose moieties in said oligo- or polynucleotide.

Claim 1441 (CURRENTLY AMENDED). The process according to claim 1440, wherein, in nucleotide or nucleotide analog structure (i), said covalent attachment is through a linkage group.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 163 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1442 (CURRENTLY AMENDED). The process according to claim 1441, wherein in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1443 (PREVIOUSLY PRESENTED). The process according to claim 1442, wherein said amine comprises a primary amine.

Claim 1444 (PREVIOUSLY PRESENTED). The process according to claim 1441, wherein said linkage group does not substantially interfere with the binding of said non-radioactively detectable protein to said protein binding sequence.

Claim 1445 (CURRENTLY AMENDED). The process according to claim 1411, wherein said non-radioactively detectable protein comprises a signalling component or indicator ~~molecule~~ moiety.

Claim 1446 (CURRENTLY AMENDED). The process according to claim 1445, wherein said signalling component or indicator ~~molecule~~ moiety comprises at least three carbon atoms.

Claim 1447 (CURRENTLY AMENDED). The process according to claim 1446, wherein said Signalling component or indicator ~~molecule~~ moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1448 (CURRENTLY AMENDED). The process according to claim 1446, wherein said Signalling component or indicator ~~molecule~~ moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1449 (CURRENTLY AMENDED). The process according to claim 1446, wherein said Signalling component or indicator ~~molecule~~ moiety comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 164 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1450 (PREVIOUSLY PRESENTED). The process according to claim 1449, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1451 (CURRENTLY AMENDED). The process according to claim 1446, wherein said Signalling component or indicator ~~molecule~~ moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1452 (PREVIOUSLY PRESENTED). The process according to claim 1451, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1453 (CURRENTLY AMENDED). The process according to claim 1446, wherein said Signalling component or indicator ~~molecule~~ moiety comprises a monosaccharide, polysaccharide or an oligosaccharide.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 165 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1454 (CURRENTLY AMENDED). The process according to claim 1445, wherein said Signalling component or indicator ~~molecule~~ moiety comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1455 (CURRENTLY AMENDED). The process according to claim 1445, wherein said Signalling component or indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 1456 (CURRENTLY AMENDED). The process according to claim 1455, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1457 (CURRENTLY AMENDED). The process according to claim 1456, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1458 (CURRENTLY AMENDED). The process according to claim 1457, wherein said fluorescent heterocyclic aromatic ~~compounds~~ structure is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1459 (CURRENTLY AMENDED). The process according to claim 1458, wherein said fluorescent heterocyclic aromatic ~~compounds~~ structure comprises fluorescein.

Claim 1460 (CURRENTLY AMENDED). The process according to claim 1454, wherein said Signalling component or indicator ~~molecule~~ moiety comprises a chemiluminescent component.

Claim 1461 (CURRENTLY AMENDED). The process according to claim 1454, wherein said Signalling component or indicator ~~molecule~~ moiety comprises a chelating component.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 166 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1462 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said non-radioactively detectable protein is detectable by a means selected from the group consisting of a fluorescent measurement and a chemiluminescent measurement, or a combination thereof.

Claim 1463 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said non-radioactively detectable protein is detectable when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex formed with said nucleic acid of interest.

Claim 1464 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said nonradioactively detectable protein is detectable when it is attached to said oligo- or polynucleotide directly or through a linkage group.

Claim 1465 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said oligo- or polynucleotide is contacted with said sample suspected of containing the nucleic acid of interest prior to forming a complex with said non-radioactively detectable protein.

Claim 1466 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said detecting step is carried out directly.

Claim 1467 (CURRENTLY AMENDED). The process according to claim 1466, wherein said direct detection of the non-radioactively detectable protein is carried out on one or more signalling components or indicator ~~molecules~~ moieties.

Claim 1468 (CURRENTLY AMENDED). The process according to claims 1467, wherein said direct detection step is carried out by a member selected from the group consisting of a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure, an enzyme, a ~~radioactive compound~~ and an electron dense ~~compound~~structure.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 167 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1469 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said detecting step is carried out indirectly.

Claim 1470 (CURRENTLY AMENDED). The process according to claim 1469, wherein said indirect detection is carried out by a means selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand, an enzyme, a ~~compound~~ structure capable of binding to an insoluble phase, and a combination of any of the foregoing.

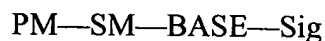
Claim 1471 (PREVIOUSLY PRESENTED). The process according to claim 1411, wherein said nonradioactively detectable protein is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 1472 (PREVIOUSLY PRESENTED). The process according to claim 1411, further comprising one or more washing steps.

Claim 1473 (CURRENTLY AMENDED). A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising ~~the~~ steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or one or more detectable non-radioactively modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

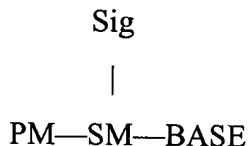
BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety ~~or an analog of any of the foregoing thereof~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine

moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

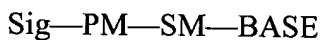
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a ~~base moiety or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group,

to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

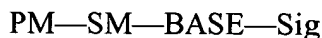
detecting non-radioactively any specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides, and determining the number of copies of said particular chromosome; and

comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

Claim 1474 (CURRENTLY AMENDED). A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising ~~the steps of~~ :

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or one or more detectable non-radioactively modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~non-radioactive~~ modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide structure or nucleotide analog structure having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

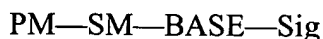
detecting non-radioactively any of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

Claim 1475 (CURRENTLY AMENDED). A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising ~~the steps of~~ :

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein said clones or fragments or said oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator ~~molecule~~ moiety and each of said clones or DNA fragments or oligo- or polynucleotides comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled ~~nucleotide~~ nucleotides or nucleotide ~~analog~~ analogs are selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

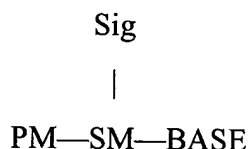
SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine ~~or a pyrimidine analog~~ , at a position other than the C8 position when BASE is a purine ~~or a purine analog~~ , and at a position other than the C7 position when BASE is a 7-deazapurine ~~or a 7-deazapurine analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

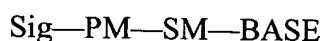
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a ~~base moiety~~ base moiety ~~or base analog~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group ;

fixing the chromosomes from or in said cell;

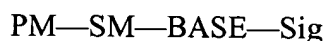
contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting non-radioactively any of said different indicator ~~molecules~~ moieties in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

Claim 1476 (CURRENTLY AMENDED). A process for determining the number of chromosomes in an interphase cell of interest, the process comprising ~~the steps of~~ :

providing sets of clones or DNA fragments or oligo- or polynucleotides derived from said clones, wherein said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest and each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprises one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactively modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

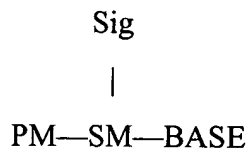
SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety ~~or a pyrimidine analog~~ , at a position other than the C8 position when BASE is a purine ~~or a purine analog~~ , and at a position other than the C7 position when BASE is a 7-deazapurine ~~or a 7-deazapurine analog~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

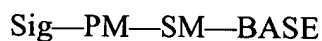
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure ~~, said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

detecting non-radioactively any of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generated signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

Claim 1477 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said nucleotide analog can be attached terminally to DNA or RNA by means of an enzyme.

Claim 1478 (PREVIOUSLY PRESENTED). The process according to claim 1477, wherein said enzyme comprises terminal transferase.

Claim 1479 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said nucleotide analog can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

Claim 1480 (PREVIOUSLY PRESENTED). The process according to claim 1479, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 1481 (PREVIOUSLY PRESENTED). The process according to claim 1479, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 180 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1482 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said incorporation comprises nick translation.

Claim 1483 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 1484 (PREVIOUSLY PRESENTED). The process according to claim 1483, wherein said polymerizing enzyme comprises a polymerase.

Claim 1485 (PREVIOUSLY PRESENTED). The process according to claim 1484, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 1486 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said PM ~~phosphate moiety or phosphate analog~~ is selected from the group consisting of a mono-phosphate, a di-phosphate, a tri-phosphate and a tetraphosphate.

Claim 1487 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises nucleoside mono-, di- or tri-phosphate.

Claim 1488 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said ~~sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Claim 1489. (CURRENTLY CANCELLED) The process according to claim 1488, wherein said monosaccharide comprises a furanose.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 181 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1490 (CURRENTLY AMENDED). The process according to claim ~~1489~~ 1473, 1474, 1475 or 1476, wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 1491 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein ~~said base moiety or base analog~~ BASE in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) is ~~selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.~~

Claim 1492 (CURRENTLY CANCELLED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) is selected from the group consisting of a pyrimidine, a purine, a 7-deazapurine, and a combination of any of the foregoing.

Claim 1493 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said ~~Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position when BASE is a purine that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 1494 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said ~~Sig detectable non-radioactive moiety~~ in said nucleotide or nucleotide analog structure (i) is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine comprises cytosine, the N<sup>2</sup> position when said purine comprises adenine or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

Claim 1495 (CURRENTLY AMENDED). The process according to claim 1489, wherein in said nucleotide or nucleotide analog structure (ii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-deazapurine, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1496 (CURRENTLY AMENDED). The process according to claim 1489, wherein in said nucleotide or nucleotide analog structure (iii), PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine or the N9 position when BASE is a purine or 7-

Dean L. Engelhardt et al.

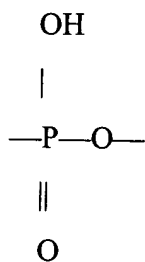
Serial No.: 08/486,069

Filed: June 7, 1995

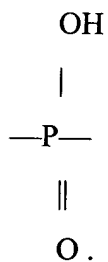
**Page 183 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

deazapurine, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1497 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of



and



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 184 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

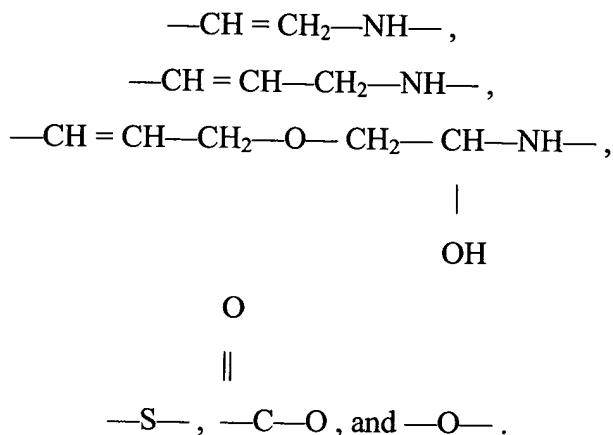
Claim 1498 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein PM is a mono-, di or tri-phosphate, and wherein said nucleotide or nucleotide analog structure (iii), the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

Claim 1499 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1500 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises a member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a —CH<sub>2</sub>NH— moiety, or both.

Claim 1501 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises an allylamine group.

Claim 1502 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or any of the moieties



Claim 1503 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) includes a glycosidic linkage moiety.

Claim 1504 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein in any of said ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) said Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 1505 (CURRENTLY AMENDED). The process according to claim 1504, wherein , in nucleotide or nucleotide analog structure (i), said linkage group contains an amine.

Claim 1506 (PREVIOUSLY PRESENTED). The process according to claim 1505, wherein said amine comprises a primary amine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 186 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1507 (PREVIOUSLY PRESENTED). The process according to claim 1504, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1508 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig comprises at least three carbon atoms.

Claim 1509 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least three carbon atoms and at least one double bond.

Claim 1510 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1511 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 1512 (PREVIOUSLY PRESENTED). The process according to claim 1511, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

Claim 1513 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1514 (PREVIOUSLY PRESENTED). The process according to claim 1513, wherein said aromatic or cycloaliphatic moiety is fluorescent or chemiluminescent.

**Enz-5(D8)(C2)**

Claim 1515 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 1516 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1517 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises an electron dense component.

Claim 1518 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein said electron dense component comprises ferritin.

Claim 1519 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a magnetic component.

Claim 1520 (PREVIOUSLY PRESENTED). The process according to claim 1519, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1521 (PREVIOUSLY PRESENTED). The process according to claim 1519, wherein said magnetic component comprises magnetic beads.

Claim 1522 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig comprises a sugar residue and the sugar residue is completed with or attached to a sugar binding protein or a polysaccharide binding protein.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 188 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1523 (PREVIOUSLY PRESENTED). The process according to claim 1522, wherein the binding protein comprises a lectin.

Claim 1524 (PREVIOUSLY PRESENTED). The process according to claim 1523, wherein the lectin comprises concanavalin A.

Claim 1525 (PREVIOUSLY PRESENTED). The process according to claim 1523, wherein said lectin is conjugated to ferritin.

Claim 1526 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises an enzyme.

Claim 1527 (PREVIOUSLY PRESENTED). The process according to claim 1526, wherein said enzyme is selected from the group consisting of alkaline phosphatase, acid phosphatase, galactosidase, ribonuclease, glucose oxidase and peroxidase, or a combination thereof.

Claim 1528 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a hormone.

Claim 1529 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a metal-containing component.

Claim 1530 (PREVIOUSLY PRESENTED). The process according to claim 1529, wherein said metal-containing component is catalytic.

Claim 1531 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig ~~detectable non-radioactive moiety~~ comprises an a non-radioactively detectable indicator molecule moiety.

**Enz-5(D8)(C2)**

Claim 1532 (CURRENTLY AMENDED). The process according to claim 1531, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 1533 (CURRENTLY AMENDED). The process according to claim 1532, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1534 (CURRENTLY AMENDED). The process according to claim 1533, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1535 (CURRENTLY AMENDED). The process according to claim 1534, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine, dansyl, and a combination of any of the foregoing.

Claim 1536 (CURRENTLY AMENDED). The process according to claim 1535, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1537 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a fluorescent component.

Claim 1538 (PREVIOUSLY PRESENTED). The process according to claim 1537, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1539 (PREVIOUSLY PRESENTED). The process according to claim 1538, wherein said fluorescent component comprises fluorescein.

Claim 1540 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a chemiluminescent component.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 190 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1541 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises an antigenic or hapten component capable of completing with an antibody specific to the component.

Claim 1542 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises an antibody component.

Claim 1543 (PREVIOUSLY PRESENTED). The process according to claim 1516, wherein Sig comprises a chelating component.

Claim 1544 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety comprises ~~an~~ a non-radioactively detectable indicator ~~molecule~~ moiety.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 191 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1545 (CURRENTLY AMENDED). The process according to claim 1544, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, and a chelating component, and a combination of any of the foregoing.

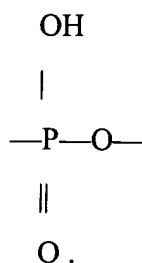
Claim 1546 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein any of nucleotide or nucleotide analogs (i), (ii) and (iii) are detectable by a means selected from the group consisting of a fluorescent measurement and a chemiluminescent measurement, or a combination thereof.

Claim 1547 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig is detectable when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

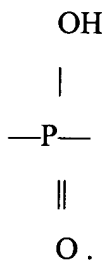
Claim 1548 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig is detectable when it is attached to the nucleotide directly or through a linkage group.

Claim 1549 (PREVIOUSLY PRESENTED). The process according to claim 1548, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

Claim 1550 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig in said nucleotide or nucleotide analog structure (iii) is covalently attached to PM via the chemical linkage



Claim 1551 (CURRENTLY AMENDED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein Sig in said nucleotide or nucleotide analog structure (iii) is covalently attached to PM via the chemical linkage



Claim 1552 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein the oligo-or polynucleotide is terminally ligated or attached to a polypeptide.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 193 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1553 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, further comprising contacting the sample with a polypeptide capable of forming a complex with Sig and a moiety which can be detected when the complex is formed.

Claim 1554 (PREVIOUSLY PRESENTED). The process according to claim 1552, wherein the polypeptide comprises a polylysine.

Claim 1555 (PREVIOUSLY PRESENTED). The process according to claim 1553, wherein the polypeptide comprises a polylysine.

Claim 1556 (PREVIOUSLY PRESENTED). The process according to claim 1552, wherein the polypeptide comprises at least one member selected from the group consisting of avidin, streptavidin or anti-Sig immunoglobulin.

Claim 1557 (PREVIOUSLY PRESENTED). The process according to claim 1553, wherein the polypeptide comprises at least one member selected from the group consisting of avidin, streptavidin or anti-Sig immunoglobulin.

Claim 1558 (PREVIOUSLY PRESENTED). The process according to claim 1553, wherein Sig comprises a ligand and the polypeptide comprises an antibody thereto.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 194 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1559 (PREVIOUSLY PRESENTED). The process according to claim 1553, wherein the moiety which can be detected when the complex is formed is selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1560 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said detecting step is carried out directly.

Claim 1561 (CURRENTLY AMENDED). The process according to claim 1560, wherein said direct detection is carried out on one or more non-radioactively detectable indicator ~~molecules~~ moieties.

Claim 1562 (CURRENTLY AMENDED). The process according to claim 1561, wherein said ~~one or more~~ non-radioactively detectable indicator ~~molecules~~ moieties comprise ~~fluorescent~~ fluorescently labeled nucleotides.

Claim 1563 (CURRENTLY AMENDED). The process according to claim 1562, wherein said ~~fluorescent~~ fluorescently labeled nucleotides ~~or nucleotide analogs~~ comprise fluorescent DNA.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 195 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1564 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said detecting step is carried out by means of a directly detectable signal provided by said Sig detectable non-radioactive moiety.

Claim 1565 (CURRENTLY AMENDED). The process according to claim 1564, wherein said detecting step is carried out by means of a member selected from the group consisting of a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure and an electron dense ~~compound~~ structure.

Claim 1566 (PREVIOUSLY PRESENTED). The process according to claim 1564, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

Claim 1567 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said Sig detectable non-radioactive moiety.

Claim 1568 (PREVIOUSLY PRESENTED). The process according to claim 1567, wherein said detecting step the indirectly detectable non-radioactive signal is provided by a member selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand and an enzyme.

Claim 1569 (PREVIOUSLY CANCELLED).

Claim 1570 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 196 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1571 (PREVIOUSLY PRESENTED). The process according to any of claims 1473, 1474, 1475 or 1476, further comprising one or more washing steps.

Claim 1572 (PREVIOUSLY PRESENTED). The process according to claim 1473, 1474, 1475 or 1476, wherein said one or more clones or DNA fragments or oligo- or polynucleotides derived from clone or clones are derived from said particular chromosome or said chromosome of interest or said chromosome in said interphase cell of interest.

Claim 1573 (CURRENTLY AMENDED). The process according to claim 1475, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides is labeled with the same indicator ~~molecule~~ moiety.

Claim 1574 (PREVIOUSLY PRESENTED). The process according to any of claims. 1473, 1474 or 1475, wherein said detecting step is carried out by a means selected from the group consisting of manual means and automatic means.

Claim 1575 (PREVIOUSLY PRESENTED). The process according to claim 1574, wherein said manual means comprises visualization.

Claim 1576 (PREVIOUSLY PRESENTED). The process according to claim 1574, wherein said automatic means comprises computerized automatic karyotyping.

Claim 1577 (CURRENTLY AMENDED). The process according to claim 1476, wherein each of said sets of clones or DNA fragments or oligo- or polynucleotides is labeled with the same indicator ~~molecule~~ moiety.

Claim 1578 (CURRENTLY AMENDED). The process according to claim 1476, wherein each of said sets of clones or DNA fragments or oligo- or polynucleotides is labeled with a different indicator ~~molecule~~ moiety.

**Enz-5(D8)(C2)**

Claim 1579 (PREVIOUSLY PRESENTED). The process according to claim 1476, wherein said detecting and determining step is carried out by a means selected from the group consisting of manual means and automatic means.

Claim 1580 (PREVIOUSLY PRESENTED). The process according to claim 1579, wherein said manual means comprises visualization.

Claim 1581 (PREVIOUSLY PRESENTED). The process according to claim 1579, wherein said automatic means comprises computerized automatic karyotyping.

Claim 1582 (CURRENTLY AMENDED). A process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest, comprising ~~the steps of~~ :

(A) providing either:

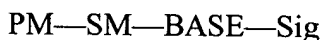
(1) one or more detectable non-radioactive chemically modified or labeled nucleotides or detectable non-radioactive chemically modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said ~~detectable non-radioactive~~ chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signalling moieties which are capable of providing directly or indirectly a detectable non-radioactive signal; or

(2) an oligo- or polynucleotide of interest comprising one or more said ~~detectable non-radioactive~~ chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic

acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides;

wherein said ~~detectable non-radioactive~~ chemically modified or labeled nucleotides or nucleotide analogs of (1) and (2) have been modified or labeled on at least one of the ~~sugar-furanose-moiety, the sugar analog~~, the phosphate moiety, ~~the phosphate moiety~~, or the base moiety or the base analog, and comprise a nucleotide structure or nucleotide analog structure are selected from the group consisting of one or more of :

(i)



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar-furanose-moiety or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety that comprises at least three carbon atoms, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

(ii)

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~ ,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive moiety that comprises at least three carbon atoms , and

wherein ~~said~~ PM is covalently attached to SM, ~~said~~ BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~ ,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a detectable non-radioactive signalling moiety that comprises at least three carbon atoms and is detected non-radioactively by an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, an electron density measurement, a magnetic measurement, or any combination of the foregoing measurements ; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

provided that when said nucleotide structure or nucleotide analog structure (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical

linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

said oligo- or polynucleotide of interest; and

(B) either incorporating said ~~one or more detectable non-radioactive~~ chemically modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a non-radioactive labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

Claim 1583 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said oligo- or polynucleotide of interest is derived from an organism.

Claim 1584 (PREVIOUSLY PRESENTED). The process according to claim 1583, wherein said organism is living.

Claim 1585 (PREVIOUSLY PRESENTED). The process according to claims 1583 or 1584, wherein the organism is selected from the group consisting of prokaryotes and eukaryotes.

Claim 1586 (PREVIOUSLY PRESENTED). The process according to claim 1585, wherein said organism comprises a eukaryote.

Claim 1587 (PREVIOUSLY PRESENTED). The process according to claim 1586, wherein said eukaryotic oligo- or polynucleotide of interest is contained within a chromosome.

Claim 1588 (PREVIOUSLY PRESENTED). The process according to claim 1586, wherein said eukaryote comprises a mammal.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 201 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1589 (PREVIOUSLY PRESENTED). The process according to claim 1588, wherein said mammalian oligo- or polynucleotide of interest is contained within a chromosome.

Claim 1590 (PREVIOUSLY PRESENTED). The process according to claim 1588, wherein said mammal comprises a human being.

Claim 1591 (PREVIOUSLY PRESENTED). The process according to claim 1590, wherein said human oligo- or polynucleotide of interest is contained within a chromosome.

Claim 1592 (PREVIOUSLY PRESENTED). The process according to claim 1591, wherein said human chromosomal oligo- or polynucleotide of interest is part of a human gene library.

Claim 1593 (PREVIOUSLY PRESENTED). The process according to claims 1583 or 1584, wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

Claim 1594 (PREVIOUSLY PRESENTED). The process according to claim 1584, wherein said living organism comprises a mammal.

Claim 1595 (PREVIOUSLY PRESENTED). The process according to claim 1594, wherein said mammal comprises a human being.

Claim 1596 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said incorporating step is carried out using an enzyme.

Claim 1597 (PREVIOUSLY PRESENTED). The process according to claim 1596, wherein said enzyme comprises a polymerase.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 202 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1598 (PREVIOUSLY PRESENTED). The process according to claim 1597, wherein said polymerase comprises DNA polymerase.

Claim 1599 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said nucleotide analog can be attached terminally to DNA or RNA by an enzyme.

Claim 1600 (PREVIOUSLY PRESENTED). The process according to claim 1599, wherein said enzyme comprises terminal transferase.

Claim 1601 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said nucleotide analog can be coupled to DNA or RNA by a coupling means selected from the group consisting of chemical coupling and enzymatic coupling.

Claim 1602 (PREVIOUSLY PRESENTED). The process according to claim 1601, wherein said chemical coupling can be carried out by a chemical coupling means selected from the group consisting of carbodiimide and formaldehyde.

Claim 1603 (PREVIOUSLY PRESENTED). The process according to claim 1601, wherein said enzymatic coupling can be carried out by an enzymatic coupling means selected from the group consisting of DNA ligase and RNA ligase.

Claim 1604 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said incorporation comprises nick translation.

Claim 1605 (PREVIOUSLY PRESENTED). The process according to claim 1582 or 1604, wherein said incorporation is carried out by means of a polymerizing enzyme.

Claim 1606 (PREVIOUSLY PRESENTED). The process according to claim 1605, wherein said polymerizing enzyme comprises a polymerase.

**Enz-5(D8)(C2)**

Claim 1607 (PREVIOUSLY PRESENTED). The process according to claim 1606, wherein said polymerase is selected from the group consisting of DNA polymerase and RNA polymerase.

Claim 1608 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said one or more detectable non-radioactive chemically modified nucleotides or said other modified or unmodified nucleic acids comprise a nucleoside di- or tri-phosphate.

Claim 1609 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said incorporating step is template dependent or template independent.

Claim 1610 (PREVIOUSLY PRESENTED). The process according to claim 1609, wherein said incorporating step is template dependent.

Claim 1611 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said labeled oligo- or polynucleotide of interest prepared by said incorporating step comprises at least one internal modified nucleotide.

Claim 1612 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said labeled oligo- or polynucleotide of interest prepared by said incorporating step comprises at least one terminal modified nucleotide.

Claim 1613 (PREVIOUSLY CANCELLED).

Claim 1614 (CURRENTLY AMENDED). The process according to claim 1582, wherein said PM phosphate moiety or phosphate analog is selected from the group consisting of a monophosphate, a di-phosphate, a tri-phosphate and a tetra-phosphate.



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 204 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1615 (CURRENTLY AMENDED). The process according to claim 1582, wherein any of said ~~nucleotides (i), (ii) or (iii) comprise~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) comprises a nucleoside mono-, di- or tri-phosphate.

Claim 1616 (CURRENTLY AMENDED). The process according to claim 1582, wherein ~~said sugar moiety or sugar analog~~ SM comprises a monosaccharide.

Claim 1617. (CURRENTLY CANCELLED) The process according to claim 1616, wherein said monosaccharide comprises a furanose.

Claim 1618 (CURRENTLY AMENDED). The process according to claim ~~1617~~ 1616, wherein ~~said furanose~~ SM is selected from the group consisting of ribose, deoxyribose and dideoxyribose.

Claim 1619 (CURRENTLY AMENDED). The process according to claim 1582, wherein ~~in said chemically modified nucleotides (i)~~ the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and Sig is covalently attached to ~~said~~ BASE at a position when BASE is a pyrimidine ~~or pyrimidine analog~~ that is selected from the group consisting of the C2 position, the N3 position, the C6 position, and combinations thereof, or is covalently attached to BASE at a position when BASE is a purine ~~or purine analog~~ that is selected from the group consisting of the N1 position, the C2 position, the N3 position, the C6 position, the N7 position, and combinations thereof.

Claim 1620 (CURRENTLY AMENDED). The process according to claim 1582, wherein ~~in said chemically modified nucleotides (i)~~ the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and Sig is covalently attached to ~~said~~ BASE at a position selected from the group consisting of the N<sup>4</sup> position when said pyrimidine ~~or pyrimidine analog~~ comprises cytosine ~~or a cytosine analog~~, the N<sup>2</sup> position when said purine ~~or purine analog~~ comprises adenine ~~, an adenine analog,~~ or deazaadenine, the N<sup>6</sup> position when said purine comprises guanine or deazaguanine, and combinations thereof.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 205 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 206 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1621 (CURRENTLY AMENDED). The process according to claim 1582, wherein ~~said base moiety or base analog~~ BASE in ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) ~~or both is selected from the group consisting of a pyrimidine, a pyrimidine analog, a purine, a purine analog, a 7-deazapurine, a 7-deazapurine analog, and a combination of any of the foregoing.~~

Claim 1622 (CURRENTLY CANCELLED). The process according to claim 1582, wherein said sugar moiety or sugar analog SM comprises a monosaccharide or a furanose, and said base moiety or base analog BASE in nucleotides (i), (ii) or (iii) or both is selected from the group consisting of a pyrimidine, a pyrimidine analog, a purine, a purine analog, a 7-deazapurine, a 7-deazapurine analog, and a combination of any of the foregoing.

Claim 1623 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) in which ~~said incorporating step, Sig in the nucleotide (i)~~ is covalently attached to BASE through a linkage group.

Claim 1624 (PREVIOUSLY PRESENTED). The process according to claim 1623, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1625 (PREVIOUSLY PRESENTED). The process according to claim 1623, wherein said linkage group contains an amine.

Claim 1626 (PREVIOUSLY PRESENTED). The process according to claim 1625, wherein said amine comprises a primary amine.

Claim 1627 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (ii) in which

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 207 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

~~said incorporating step, Sig in the nucleotide (ii)~~ is covalently attached to SM through a linkage group.

Claim 1628 (PREVIOUSLY PRESENTED). The process according to claim 1627, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1629 (CURRENTLY CANCELLED). The process according to claim 1627, wherein said linkage group contains an amine.

Claim 1630 (CURRENTLY CANCELLED). The process according to claim 1629, wherein said amine comprises a primary amine.

Claim 1631 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (iii) in which ~~said incorporating step, Sig in the nucleotide (iii)~~ is covalently attached to PM through a linkage group.

Claim 1632 (PREVIOUSLY PRESENTED). The process according to claim 1631, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1633 (CURRENTLY CANCELLED). The process according to claim 1631, wherein said linkage group contains an amine.

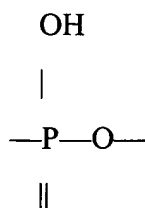
Claim 1634 (CURRENTLY CANCELLED). The process according to claim 1633, wherein said amine comprises a primary amine.

**Enz-5(D8)(C2)**

Claim 1635 (CURRENTLY AMENDED). The process according to claim 1617, wherein the nucleotide or nucleotide analog structure is in said nucleotide or nucleotide analog structure (ii), and wherein PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine ~~or a pyrimidine analog~~, or the N9 position when BASE is a purine or, ~~a purine analog~~, 7-deazapurine, ~~or a 7-deazapurine analog~~, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1636 (CURRENTLY AMENDED). The process according to claim 1617, wherein the nucleotide or nucleotide analog structure is in said nucleotide or nucleotide analog structure (iii), and wherein PM is attached to ~~said furanose~~ SM at a position independently selected from the group consisting of the 2', 3', and 5' positions, or any combination thereof, and BASE is attached to the 1' position of ~~said furanose~~ SM from the N1 position when BASE is a pyrimidine ~~or a pyrimidine analog~~, or the N9 position when BASE is a purine or, ~~a purine analog~~, 7-deazapurine, ~~or a 7-deazapurine analog~~, and Sig is covalently attached to PM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization.

Claim 1637 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (iii), and wherein said covalent attachment in nucleotide or nucleotide analog structure (iii) is selected from the group consisting of





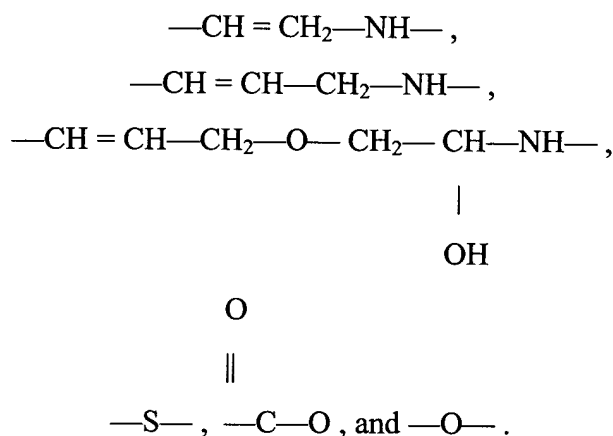
Claim 1638 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (iii), and wherein PM is a mono-, di or tri-phosphate, and ~~wherein in said nucleotide or nucleotide analog (iii)~~, the Sig moiety is covalently attached to PM through a phosphorus or phosphate oxygen.

Claim 1639 (CURRENTLY AMENDED). The process according to claim 1582, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1640 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and said covalent attachment in ~~any of nucleotides (i), (ii) or (iii)~~ comprises a member selected from the group consisting of : a —CH<sub>2</sub>NH— moiety, an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i) , a —CH<sub>2</sub>NH— moiety, or both.

Claim 1641 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and said covalent attachment ~~in any of nucleotides (i), (ii) or (iii)~~ comprises an allylamine group.

Claim 1642 (CURRENTLY AMENDED). The process according to claim 1582, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and said covalent attachment in any of nucleotides (i), (ii) or (iii) comprises or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide or nucleotide analog structure (i), or any of the moieties



Claim 1643 (CURRENTLY AMENDED). The process according to claim 1582, wherein said covalent attachment in any of ~~nucleotides~~ nucleotide or nucleotide analog structure (i), (ii) or (iii) includes a glycosidic linkage moiety.

Claim 1644 (CURRENTLY AMENDED). The process according to claim 1582, wherein in said nucleotide or nucleotide analog structure (i), (ii) or (iii), Sig is covalently attached to BASE, SM or PM through a linkage group.

Claim 1645 (CURRENTLY AMENDED). The process according to claim 1644, wherein the nucleotide or nucleotide analog structure is nucleotide or nucleotide analog structure (i) and said linkage group contains an amine.

Claim 1646 (PREVIOUSLY PRESENTED). The process according to claim 1645, wherein said amine comprises a primary amine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 211 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1647 (PREVIOUSLY PRESENTED). The process according to claim 1645, wherein said linkage group does not substantially interfere with formation of the signalling moiety or detection of the detectable non-radioactive signal.

Claim 1648 (CURRENTLY CANCELLED). The process according to claim 1582, wherein said Sig comprises at least three carbon atoms.

Claim 1649 (CURRENTLY AMENDED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising ~~at least three carbon atoms and~~ at least one double bond.

Claim 1650 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety comprises an aliphatic chemical moiety comprising at least four carbon atoms.

Claim 1651 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least five carbon atoms.

Claim 1652 (CURRENTLY AMENDED). The process according to claim 1651, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1653 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety comprises an aromatic or cycloaliphatic group comprising at least six carbon atoms.

Claim 1654 (CURRENTLY AMENDED). The process according to claim 1653, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 212 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1655 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig comprises a monosaccharide, polysaccharide or an oligosaccharide.

Claim 1656 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig comprises a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1657 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises an electron dense component.

Claim 1658 (PREVIOUSLY PRESENTED). The process according to claim 1657, wherein said electron dense component comprises ferritin.

Claim 1659 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a magnetic component.

Claim 1660 (PREVIOUSLY PRESENTED). The process according to claim 1659, wherein said magnetic component comprises magnetic oxide or magnetic iron oxide.

Claim 1661 (PREVIOUSLY PRESENTED). The process according to claim 1659, wherein said magnetic component comprises magnetic beads.

Claim 1662 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig comprises a sugar residue and the sugar residue is complexed with or attached to a sugar binding protein or a polysaccharide binding protein.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 213 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1663 (PREVIOUSLY PRESENTED). The process according to claim 1662, wherein the binding protein comprises a lectin.

Claim 1664 (PREVIOUSLY PRESENTED). The process according to claim 1663, wherein the lectin comprises concanavalin A.

Claim 1665 (PREVIOUSLY PRESENTED). The process according to claim 1663, wherein said lectin is conjugated to ferritin.

Claim 1666 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises an enzyme.

Claim 1667 (PREVIOUSLY PRESENTED). The process according to claim 1666, wherein said enzyme is selected from the group consisting of alkaline phosphatase, acid phosphatase, galactosidase, ribonuclease, glucose oxidase and peroxidase, or a combination thereof.

Claim 1668 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a hormone.

Claim 1669 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a metal-containing component.

Claim 1670 (PREVIOUSLY PRESENTED). The process according to claim 1669, wherein said metal-containing component is catalytic.

Claim 1671 (CURRENTLY AMENDED). The process according to claim 1582, wherein said Sig ~~detectable non-radioactive moiety~~ comprises ~~an~~ a non-radioactively detectable indicator molecule moiety.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 214 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

Claim 1672 (CURRENTLY AMENDED). The process according to claim 1671, wherein said indicator ~~molecule~~ moiety comprises an aromatic ~~compound~~ structure.

Claim 1673 (CURRENTLY AMENDED). The process according to claim 1672, wherein said aromatic ~~compound~~ structure is heterocyclic.

Claim 1674 (CURRENTLY AMENDED). The process according to claim 1673, wherein said heterocyclic aromatic ~~compound~~ structure is fluorescent.

Claim 1675 (CURRENTLY AMENDED). The process according to claim 1674, wherein the fluorescent heterocyclic aromatic ~~compound~~ structure is selected from the group consisting of fluorescein, rhodamine and dansyl.

Claim 1676 (CURRENTLY AMENDED). The process according to claim 1675, wherein said fluorescent heterocyclic aromatic ~~compound~~ structure comprises fluorescein.

Claim 1677 (CURRENTLY AMENDED). The process according to claim 1671, wherein said indicator ~~molecule~~ moiety comprises a member selected from the group consisting of a fluorescent component, a chromogenic component, a chemiluminescent component, and a chelating component, and a combination of any of the foregoing.

Claim 1678 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a fluorescent component.

Claim 1679 (PREVIOUSLY PRESENTED). The process according to claim 1678, wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 215 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1680 (PREVIOUSLY PRESENTED). The process according to claim 1679, wherein said fluorescent component comprises fluorescein.

Claim 1681 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a chemiluminescent component.

Claim 1682 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises an antigenic or hapten component capable of completing with an antibody specific to the component.

Claim 1683 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises an antibody component.

Claim 1684 (PREVIOUSLY PRESENTED). The process according to claim 1656, wherein said Sig comprises a chelating component.

Claim 1685 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein any of nucleotide or nucleotide analogs (i), (ii) and (iii) are detectable by a means selected from the group consisting of a fluorescent measurement and a chemiluminescent measurement, or a combination thereof.

Claim 1686 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig is detectable non-radioactively when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

Claim 1687 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig is detectable non-radioactively when it is attached to the nucleotide directly or through a linkage group.

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 216 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1688 (PREVIOUSLY PRESENTED). The process according to claim 1687, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

Claim 1689 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said labeled oligo- or polynucleotide of interest is terminally ligated or attached to a polypeptide.

Claim 1690 (PREVIOUSLY PRESENTED). The process according to claim 1689, further comprising contacting the sample with a polypeptide capable of forming a complex with Sig and a moiety which can be detected when the complex is formed.

Claim 1691 (PREVIOUSLY PRESENTED). The process according to claim 1689, wherein the polypeptide comprises a polylysine.

Claim 1692 (PREVIOUSLY PRESENTED). The process according to claim 1689, wherein the polypeptide comprises at least one member selected from the group consisting of avidin, streptavidin or anti-Sig immunoglobulin.

Claim 1693 (PREVIOUSLY PRESENTED). The process according to claim 1690, wherein said Sig comprises a ligand and the polypeptide comprises an antibody thereto.

Claim 1694 (PREVIOUSLY PRESENTED). The process according to claim 1690, wherein the moiety which can be detected when the complex is formed is selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1695 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being directly detected.

Claim 1696 (CURRENTLY AMENDED). The process according to claim 1695, wherein said directly detectable signal providing Sig detectable non-radioactive moiety is selected from the group consisting of a fluorogenic ~~compound~~ structure, a chromogenic ~~compound~~ structure, a chemiluminescent ~~compound~~ structure, an electron dense ~~compound~~ structure and an enzyme.

Claim 1697 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being indirectly detected.

Claim 1698 (PREVIOUSLY PRESENTED). The process according to claim 1697, wherein said detecting step the indirectly detectable signal is provided by a member selected from the group consisting of an antibody, an antigen, a hapten, a receptor, a ligand, an enzyme and a combination of any of the foregoing.

Claim 1699 (PREVIOUSLY PRESENTED). The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 1700 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising ~~the steps of~~ :

providing or generating non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof, wherein each of said fragments comprises one or more detectable ~~non-radioactive non-radioactively~~ modified or labeled nucleotides or detectable non-radioactively modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 218 Amendment** [Following Office Action of July 1, 2003] - **December 31, 2003**

nucleotide analogs comprise one or more chelating ~~compounds~~ structure or chelating components capable of chelating a metal or metal ion and providing a detectable signal, and wherein said ~~one or more detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the ~~sugar~~ furanose moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety, ~~or the base analog thereof~~ ;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting the presence of each of said separated or resolved fragments by detecting the means of the detectable signal provided by a metal or metal ion chelated by said chelating ~~compounds~~ structure or chelating components ~~in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs~~; and

determining the sequence of said nucleic acid of interest.

Claim 1701. (CURRENTLY AMENDED) A process for determining the sequence of a nucleic acid of interest, comprising ~~the steps of~~ :

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs comprise one or more chelating ~~compounds~~ structure or chelating components capable of chelating a metal or metal ion and providing a detectable signal, and wherein said ~~one or more~~ detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the ~~sugar~~ furanose moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety, ~~or the base analog thereof~~ ;

introducing or subjecting said fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting each of the separated or resolved fragments by ~~means of the detectable~~ detecting the signal provided by a metal or metal ion chelated by said chelating ~~compounds~~ structure or chelating components in the ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs ; and

determining the sequence of said nucleic acid of interest.

Claim 1702. (CURRENTLY AMENDED) A process for determining the sequence of a nucleic acid of interest, comprising ~~the steps of~~ :

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs comprise one or more chelating ~~compounds~~ structure or chelating components capable of chelating a metal or metal ion and providing a detectable signal, and wherein said ~~one or more~~ detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar-furanose-moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety ~~or the base analog thereof~~ ;

detecting with a sequencing gel the detectable non-radioactive labeled nucleic acid fragments by means of a metal or metal ion chelated by said chelating ~~compounds~~ structure or chelating components; and

determining the sequence of said nucleic acid of interest.



Claim 1703. (CURRENTLY AMENDED) A process for determining the sequence of a nucleic acid of interest, comprising ~~the step of~~ detecting with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs comprise one or more chelating ~~compounds~~ structure or chelating components capable of chelating a metal or metal ion and providing a detectable signal, and wherein said ~~one or more detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar-furanose moiety, ~~the sugar analog~~, the phosphate moiety, or the base moiety ~~or the base analog thereof~~.

Claim 1704. (CURRENTLY AMENDED) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising ~~the steps of~~ :

(A) providing

(1) ~~(i)~~ one or more detectable non-radioactive chemically modified or chemically labeled nucleotides or detectable non-radioactive chemically modified or chemically labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or

(2) ~~(ii)~~ one or more oligonucleotides or polynucleotides comprising at least one of said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (i) ; or

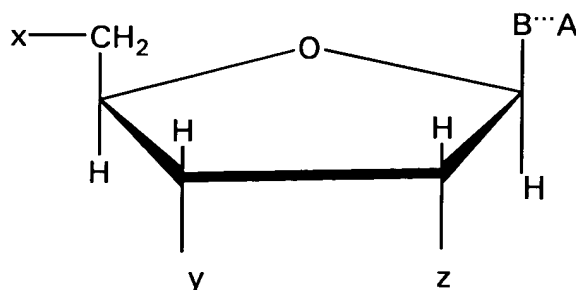
(3) ~~(iii)~~ both ~~(i) and (ii)~~ (1) and (2) ;

wherein said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs ~~(i)~~ (1) and said oligonucleotides and polynucleotides ~~(ii)~~ (2) are capable of attaching to or coupling to or incorporating into or forming one or more

nucleic acid fragments, wherein said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (1) comprise one or more chelating compounds structure or chelating components capable of chelating a metal or metal ion and providing a detectable signal, and wherein said ~~detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (1) have been non-radioactively modified or non-radioactively labeled, non-disruptively or disruptively, on at least one of the sugar furanose moiety, the sugar analog, the phosphate moiety, the phosphate analog, or the base moiety or the base analog thereof; and ;

(B) incorporating said ~~one or more detectable non-radioactive chemically modified or labeled~~ nucleotides or nucleotide analogs (1) or said ~~one or more~~ oligonucleotides or polynucleotides (2) ~~comprising at least one of said detectable non-radioactive chemically modified or labeled~~ nucleotides (ii), or both (i) and (ii) (1) and (2), into said ~~one or more~~ nucleic acid fragments, to ~~prepare detectable non-radioactive labeled fragments~~, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, ~~said detectable non-radioactive labeled fragments further comprising~~ and wherein said nucleotides or nucleotide analogs (1) comprise a one or more detectable non-radioactive chemically modified nucleotides or nucleotide analogs or labeled nucleotide structure, or detectable non-radioactive chemically modified or labeled nucleotide analog structure, selected from the group consisting of one or more of :

(i)



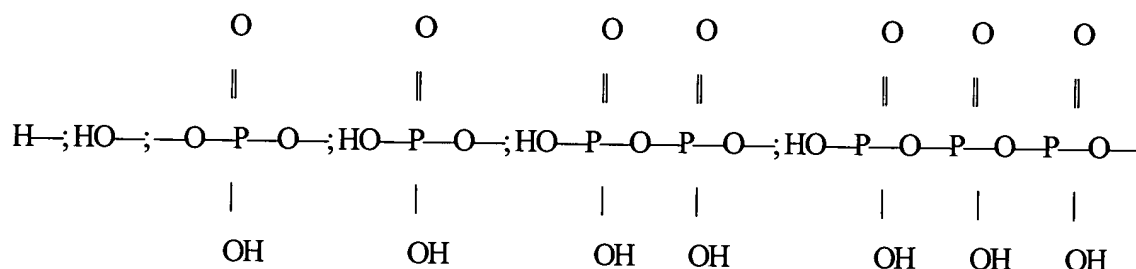
wherein B represents a purine moiety, a 7-deazapurine moiety, or a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar furanose moiety or sugar analog, provided that whenever B is a purine, a purine analog, or a 7-

deazapurine moiety ~~or a 7-deazapurine analog~~, the ~~sugar-furanose-moiety or sugar analog~~ is attached at the N9 position of the purine moiety, ~~the purine analog, the, or the~~ 7-deazapurine moiety ~~or the 7-analog thereof~~, and whenever B is a pyrimidine moiety ~~or a pyrimidine analog~~, the ~~sugar-furanose-moiety or sugar analog~~ is attached at the N1 position of the pyrimidine moiety ~~or the pyrimidine analog~~;

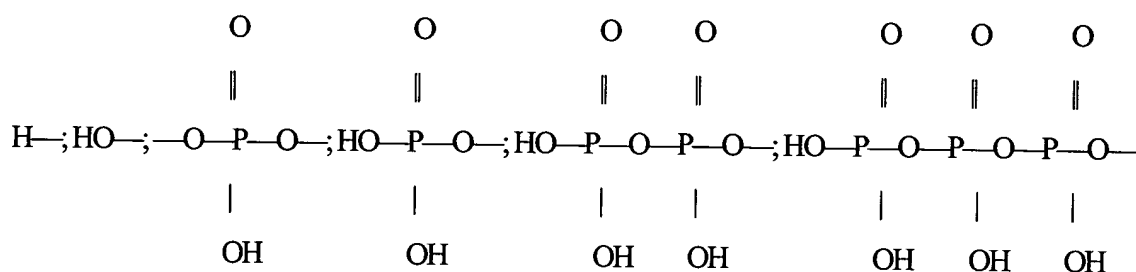
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing directly or indirectly a detectable signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



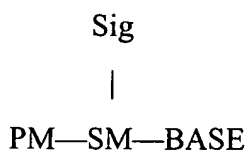
wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of

H- and HO-

(ii)



wherein

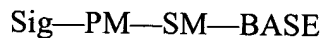
PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, and wherein ~~said~~ PM is covalently attached to SM, ~~said~~ BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~,

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said labeled fragments to a sequencing gel;

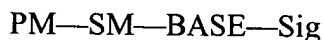
(D) separating or resolving said labeled fragments; and

(E) detecting directly or indirectly the presence of said labeled fragments by means of a metal or metal ion chelated by said chelating ~~compounds~~ structure or chelating components.

Claim 1705 (CURRENTLY AMENDED). A process for detecting a nucleic acid of interest in a sample, which process comprises ~~the steps of~~ :

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs comprise a nucleotide structure or nucleotide analog structure are selected from the group consisting of one or more of :

(i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

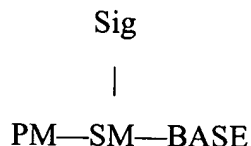
SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety ~~or a base analog of any of the foregoing~~; and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~ , at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~ and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an~~

analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

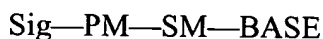
PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compounds~~ structure or component capable of providing chelating a metal or metal ion and a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

- (iii) a nucleotide structure or nucleotide analog structure, ~~said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or components capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog structure (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2', 3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting the presence of ~~said Signalling moieties~~ Sig in any of the oligo- or polynucleotides which have hybridized to said nucleic acid of interest by means of a metal or metal ion chelated by said chelating ~~compounds~~ structure or chelating components.

Claim 1706 (CURRENTLY AMENDED). A process for detecting a nucleic acid of interest in a sample, which process comprises ~~the steps of~~ :

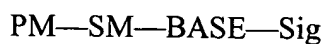
- (A) providing:
  - (i) an oligo- or polynucleotide having two segments:
    - (a) a first segment complementary to and capable of hybridizing to a portion of said nucleic acid of interest; and
    - (b) a second segment comprising at least one protein binding sequence; and
  - (ii) a detectable protein capable of binding to said protein binding sequence and comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal;
- (B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide and said detectable protein (ii) to form a complex;

(C) detecting the presence of said protein in said complex and said nucleic acid of interest by means of a metal or metal ion chelated by said chelating ~~compound~~ structure or chelating component.

Claim 1707. (CURRENTLY AMENDED) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising ~~the steps of~~ :

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or detectable non-radioactive modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactive~~ modified or labeled nucleotides or nucleotide analogs comprise a nucleotide structure or nucleotide analog structure are selected from the group consisting of one or more of :

(i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety ~~or an analog of any of the foregoing thereof~~ , and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein

**Enz-5(D8)(C2)**



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 228 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide structure or nucleotide analog structure having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~, (

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting the signal generated by said specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides by means of a metal or metal ion chelated by said chelating ~~compound~~ structure or chelating component, and determining the number of copies of said particular chromosome; and

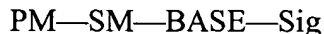
comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome ; and

determining whether the number of copies of said particular chromosome in said cell is abnormal.

Claim 1708 (CURRENTLY AMENDED). A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising ~~the steps of~~ :

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or detectable modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs comprise a nucleotide structure or nucleotide analog structure ~~are~~ selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

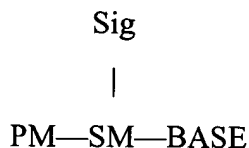
PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

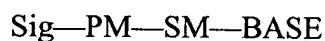
PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose-moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

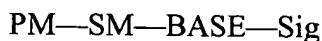
detecting by means of a metal or metal ion chelated by said chelating ~~compound~~ structure or chelating component any signal generated by each of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

Claim 1709 (CURRENTLY AMENDED). A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising ~~the steps of~~ :

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator ~~molecule~~ moiety and each of said clones or DNA fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or detectable modified or labeled nucleotide analogs capable of detection, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analogs comprise a nucleotide structure or nucleotide analog structure ~~are~~ selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

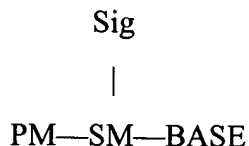
SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine. ~~or a pyrimidine analog~~ , at a position other than the C8

position when BASE is a purine ~~or a purine analog~~, and at a position other than the C7 position when BASE is a 7-deazapurine ~~or a 7-deazapurine analog thereof~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

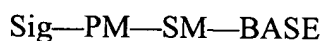
PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a base moiety ~~or base analog~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein



Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 236 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Sig comprises at least three carbon atoms, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

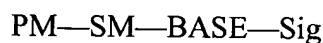
contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting by means of a metal or metal ion chelated by said chelating ~~compound~~ structure or chelating component any signal generated by each of said different indicator ~~molecules~~ moieties in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

Claim 1710 (CURRENTLY AMENDED). A process for determining the number of chromosomes in an interphase cell of interest, the process comprising ~~the steps of~~ :

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprise one or more detectable modified or labeled nucleotides or detectable modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analog comprise a nucleotide structure or nucleotide analog structure ~~are~~ selected from the group consisting of one or more of :

- (i) a nucleotide structure or nucleotide analog structure having the formula



wherein

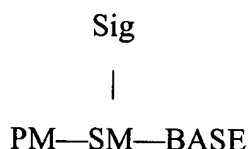
PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a, pyrimidine moiety ~~or a pyrimidine analog~~ , at a position other than the C8 position when BASE is a purine ~~or a purine analog~~ , and at a position other than the C7 position when BASE is a 7-deazapurine ~~or a 7-deazapurine analog~~;

- (ii) a nucleotide structure or nucleotide analog structure having the formula



wherein

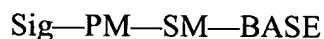
PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide structure or nucleotide analog structure , ~~said nucleotide~~ having the formula



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 239 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

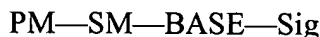
detecting by means of a metal or metal ion chelated by said chelating ~~compound~~ structure or chelating component any signals generated by each of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generate signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

Claim 1711 (CURRENTLY AMENDED). A process for preparing a labeled oligo- or polynucleotide of interest, comprising ~~the steps of~~ :

(A) providing either:

- (1) one or more detectable chemically modified or labeled nucleotides or detectable chemically modified or labeled nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said ~~chemically~~ modified or labeled nucleotides or nucleotide analogs comprise one or more signalling moieties comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, or
- (2) an oligo- or polynucleotide of interest comprising one or more of said ~~detectable chemically~~ modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said ~~chemically~~ modified or labeled nucleotides or nucleotide analogs are modified on at least one of the sugar-furanose moiety, the sugar analog, the phosphate moiety, the phosphate analog, or the base moiety or the base analog, and wherein the modified or labeled nucleotides or nucleotide analogs comprise a nucleotide structure or nucleotide analog structure ~~are~~ selected from the group consisting of one or more of :

(i)



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar-furanose-moiety or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal, wherein Sig comprises at least three carbon atoms, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety ~~or an analog thereof~~, at a position other than the C8 position when BASE is a purine moiety ~~or an analog thereof~~, and at a position other than the C7 position when BASE is a 7-deazapurine moiety ~~or an analog thereof~~;

(ii)

Sig

|



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

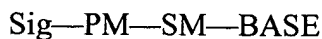
SM is a ~~sugar-furanose-moiety or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a signal, wherein Sig comprises at least three carbon atoms, and wherein ~~said~~ PM is covalently attached to SM, ~~said~~

BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety ~~or phosphate analog~~ ,

SM is a ~~sugar~~ furanose moiety ~~or sugar analog~~,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, ~~or a base analog of any of the foregoing~~, and

Sig is a signalling moiety comprising a chelating ~~compound~~ structure or chelating component capable of chelating a metal or metal ion and providing a detectable signal; wherein Sig comprises at least three carbon atoms, and wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, provided that when said nucleotide or nucleotide analog structure (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and said oligo- or polynucleotide of interest; and

(B) either incorporating said ~~one or more~~ modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

Claim 1712 (CURRENTLY AMENDED). A process for detecting the presence of a nucleic acid of interest in a sample, comprising ~~the steps of~~ :

providing or generating (i) one or more detectable non-radioactively labeled oligonucleotides or polynucleotides, each of said detectable non-radioactively labeled oligonucleotides or polynucleotides comprising a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to specifically hybridize therewith, wherein said ~~one or more~~ detectable non-radioactively labeled oligonucleotides or polynucleotides comprise one or more detectable non-radioactively modified or labeled nucleotides or detectable non-radioactively modified or labeled nucleotide analogues analogs , which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said ~~detectable non-radioactively~~ modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar-furanose-moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety, ~~or the base analog thereof~~, and (ii) a sample that may contain said nucleic acid of interest;

forming in liquid phase hybrids comprising said ~~one or more~~ detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest;

separating or resolving in a gel said formed hybrids; and

detecting non-radioactively the separated or resolved hybrids to detect the presence of said nucleic acid of interest.

Claim 1713 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein after said hybrid forming step, the liquid phase is subjected to nuclease treatment.

Claim 1714 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA.



Claim 1715 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said one or more detectable oligonucleotides or polynucleotides are selected from the group consisting of DNA, RNA and DNA-RNA.

Claim 1716 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said one or more detectable oligonucleotides or polynucleotides comprise a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chromogenic component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component.

Claim 1717 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said non-radioactive detection step is carried out directly or indirectly.

Claim 1718 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said detecting step is carried out by means of a member selected from the group consisting of enzymatic measurement, a fluorescent measurement, a chromogenic measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Claim 1719 (PREVIOUSLY PRESENTED). The process according to claim 569, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA.

Claim 1720 (PREVIOUSLY PRESENTED). The process according to claim 721, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA.

Claim 1721 (PREVIOUSLY PRESENTED). The process according to claim 873, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 245 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1722 (PREVIOUSLY PRESENTED). The process according to claim 1025, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA.

Claim 1723 (CURRENTLY AMENDED). The process according to any of claims 710, 862, 1014 or 1166, wherein said direct detection is carried out with the same indicator ~~molecules~~ moieties.

Claim 1724 (CURRENTLY AMENDED). The process according to any of claims 710, 862, 1014 or 1166, wherein said direct detection is carried out with different indicator ~~molecules~~ moieties.

Claim 1725 (CURRENTLY AMENDED). The process according to claim 1400, wherein said direct detection is carried out with the same indicator ~~molecules~~ moieties.

Claim 1726 (CURRENTLY AMENDED). The process according to claim 1400, wherein said direct detection is carried out with different indicator ~~molecules~~ moieties.

Claim 1727 (PREVIOUSLY PRESENTED). The process according to claim 1712, wherein said detecting step comprises localizing said separated or resolved hybrids.

Claim 1728 (CURRENTLY AMENDED). The process of any of claims 1700, 1701, 1702 or 1704, wherein in said providing step, the chelating ~~compounds~~ structure or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1729 (CURRENTLY AMENDED). The process of claim 1703, wherein said detecting step, the chelating ~~compounds~~ structure or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

**Enz-5(D8)(C2)**

Claim 1730 (CURRENTLY AMENDED). The process of claim 1705, wherein said specific hybridizing step, the chelating ~~compounds~~ structure or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1731 (CURRENTLY AMENDED). The process of claim 1707, wherein said contacting step, the chelating ~~compounds~~ structure or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1732 (CURRENTLY AMENDED). The process of any of claims 1700, 1701, 1702, 1703 or 1704, wherein said detecting step is carried out by a ~~compounds~~ structure or component that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1733 (CURRENTLY AMENDED). The process of any of claims 1700, 1701, 1702, 1703 or 1704, wherein in said detecting step, the chelating ~~compounds~~ structure or chelating components have chelated a metal or metal ion selected from the group consisting of heavy metals and rare earth metals.

Claim 1734 (PREVIOUSLY PRESENTED). The process of claim 1733, wherein said heavy metal comprises cobalt.

Claim 1735 (PREVIOUSLY PRESENTED). The process of claim 1732, wherein said detecting step is carried out radioactively.

Claim 1736 (PREVIOUSLY PRESENTED). The process of claim 1735, wherein said radioactive detection is carried out by means of an isotope.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 247 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1737 (PREVIOUSLY PRESENTED). The process of claim 1736, wherein said isotope is a  $\beta$  or  $\gamma$  emitter.

Claim 1738 (PREVIOUSLY PRESENTED). The process of claim 1735, wherein said radioactive detection is carried out with an isotope selected from the group consisting of bismuth-206, bismuth-207, cobalt-60, gadolinium-153, strontium-90 and yttrium-90.

Claim 1739 (PREVIOUSLY PRESENTED). The process of any of claims 638, 640, 674, 676, 790, 792, 826, 828, 942, 944, 978, 980, 1094, 1096, 1130 or 1132, wherein said fluorescent aromatic or cycloaliphatic group comprises a fluorescent dye.

Claim 1740 (CURRENTLY AMENDED). The process of any of claims 657, 693, 809, 845, 961, 997, 1113, 1149, or 1287, wherein said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs are labeled with the same indicator ~~molecules~~ moieties.

Claim 1741 (CURRENTLY AMENDED). The process of any of claims 657, 693, 809, 845, 961, 997, 1113, 1149, or 1287, wherein said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs are labeled with different indicator ~~molecules~~ moieties.

Claim 1742 (CURRENTLY AMENDED). The process of any of claims 583, 735, 887 or 1039, wherein said primers or said nucleoside triphosphates ~~or analogs thereof~~ are labeled.

Claim 1743 (CURRENTLY AMENDED). The process of any of claims 569, 721, 873, 1025, 1177, 1700, 1701, 1702, 1703 or 1704, wherein said base ~~analog~~ ~~are selected from the group consisting of analogs of~~ is a pyrimidine or a ; purine and 7-deazapurine.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 248 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1744 (CURRENTLY AMENDED). The process of claim 1743, wherein said pyrimidine ~~analog~~s ~~are~~ is selected from the group consisting of thymidine ~~analog~~s , uridine ~~analog~~s , deoxyuridine ~~analog~~s , cytidine ~~analog~~s and deoxycytidine ~~analog~~s .

Claim 1745 (CURRENTLY AMENDED). The process of claim 1744, wherein said uridine ~~analog~~s comprises ~~comprise~~ 5-bromo-2'-deoxyuridine-5'-phosphate.

Claim 1746 (CURRENTLY AMENDED). The process of claim 1744, wherein said deoxycytidine ~~analog~~s comprises ~~comprise~~ 5-hydroxymethyl-2'-deoxycytidylic acid.

Claim 1747 (CURRENTLY AMENDED). The process of claim 1743, wherein said purine ~~analog~~s ~~are~~ is selected from the group consisting of adenosine ~~analog~~s, deoxyadenosine ~~analog~~s, guanosine ~~analog~~s and deoxyguanosine ~~analog~~s.

Claim 1748 (CURRENTLY AMENDED). The process of claim 1747, wherein said adenosine ~~analog~~s ~~are~~ is selected from the group consisting of tubercidin and toyocamycin.

Claim 1749 (CURRENTLY AMENDED). The process of any of claims 1706, 1708, 1709, 1710 or 1711, wherein in said providing step, the chelating ~~compound~~s structure or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1750 (CURRENTLY AMENDED). The process of any of claims 1705, 1706, 1707, 1708, 1709, 1710 or 1711, wherein said detecting step is carried out by a ~~compound~~s structure or component that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

Claim 1751 (CURRENTLY AMENDED). The process of any of claims 1705, 1706, 1707, 1708, 1709, 1710 or 1711, wherein in said detecting step, the chelating ~~compound~~s structure or

**Enz-5(D8)(C2)**

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 249 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

chelating components have chelated a metal or metal ion selected from the group consisting of heavy metals and rare earth metals.

Claim 1752 (PREVIOUSLY PRESENTED). The process of claim 1751, wherein said heavy metal comprises cobalt.

Claim 1753 (PREVIOUSLY PRESENTED). The process of claim 1750, wherein said detecting step is carried out radioactively.

Claim 1754 (PREVIOUSLY PRESENTED). The process of claim 1753, wherein said radioactive detection is carried out by means of an isotope.

Claim 1755 (PREVIOUSLY PRESENTED). The process of claim 1754, wherein said isotope is a  $\beta$  or  $\gamma$  emitter.

Claim 1756 (PREVIOUSLY PRESENTED). The process of claim 1753, wherein said radioactive detection is carried out with an isotope selected from the group consisting of bismuth-206, bismuth-207, cobalt-60, gadolinium-153, strontium-90 and yttrium-90.

Claim 1757 (PREVIOUSLY PRESENTED). The process of any of claims 1354, 1356, 1450, 1452, 1512, 1514, 1652 or 1654, wherein said fluorescent aromatic or cycloaliphatic group comprises a fluorescent dye.

Claim 1758 (CURRENTLY AMENDED). The process of claims 1373 or 1671, wherein said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs are labeled with the same indicator ~~molecules~~ moieties.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 250 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1759 (CURRENTLY AMENDED). The process of claims 1373 or 1671, wherein said ~~non-radioactively~~ modified or labeled nucleotides or nucleotide analogs are labeled with different indicator ~~molecules~~ moieties.

Claim 1760 (CURRENTLY AMENDED). The process of any of claims 1298, 1473, 1474, 1475, 1476, 1582, 1705, 1706, 1707, 1708, 1709, 1710, 1711 or 1712, wherein said base ~~analog~~s are is selected from the group consisting of analogs of pyrimidine or ; purine and 7-deazapurine.

Claim 1761 (CURRENTLY AMENDED). The process of claim 1760, wherein said pyrimidine ~~analog~~s are is selected from the group consisting of thymidine ~~analog~~s , uridine ~~analog~~s , deoxyuridine ~~analog~~s , cytidine ~~analog~~s and deoxycytidine ~~analog~~s .

Claim 1762 (CURRENTLY AMENDED). The process of claim 1761, wherein said uridine ~~analog~~s ~~comprise~~ comprises 5-bromo-2'-deoxyuridine-5'-phosphate.

Claim 1763 (CURRENTLY AMENDED). The process of claim 1761, wherein said deoxycytidine ~~analog~~s ~~comprise~~ comprises 5-hydroxymethyl-2'-deoxycytidylic acid.

Claim 1764 (CURRENTLY AMENDED). The process of claim 1760, wherein said purine ~~analog~~s are is selected from the group consisting of adenosine ~~analog~~s , deoxyadenosine ~~analog~~s , guanosine ~~analog~~s and deoxyguanosine ~~analog~~s .

Claim 1765 (CURRENTLY AMENDED). The process of claim 1764, wherein said adenosine ~~analog~~s are is selected from the group consisting of tubercidin and toyocamycin.

Claim 1766 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest, comprising ~~the steps of~~ :

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion

**Enz-5(D8)(C2)**

thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides ~~or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA ;~~

subjecting said detectable non-radioactively labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively the presence of each of said separated or resolved fragments by detecting the ~~means of said detectable non-radioactively~~ modified or labeled nucleotides ~~or nucleotide analogs~~; and

determining the sequence of said nucleic acid of interest.

Claim 1767 (CURRENTLY AMENDED). A process for detecting non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:

providing or generating detectable non-radioactively labeled nucleic acid fragments, wherein each of said fragments comprises one or more nucleotides ~~or nucleotide analogs, which nucleotides or nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA~~, and wherein said one or more nucleotides ~~or nucleotide analogs~~ comprise one or more fluorescent, chromogenic or chemiluminescent indicators on at least one of the sugar-furanose moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety, ~~or the base analog thereof~~;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively each of said separated or resolved fragments by detecting ~~means of~~ the fluorescent, chromogenic or chemiluminescent indicators.

Claim 1768 (CURRENTLY AMENDED). A process for resolving or separating non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:

providing or generating detectable non-radioactively labeled nucleic acid fragments comprising one or more nucleotides ~~or nucleotide analogs~~ that can be attached to or coupled to or incorporated into DNA or RNA, and wherein one or more fluorescent or chromogenic



~~chemiluminescent~~ indicators are covalently attached, directly or through a linkage group, to at least one of the ~~sugar~~ furanose-moiety, ~~the sugar analog~~, the phosphate moiety, ~~the phosphate analog~~, or the base moiety ~~or the base analog~~ of said nucleotides ~~or nucleotide analogs~~ ;

· subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively each of said separated or resolved fragments by means of the fluorescent or chromogenic ~~chemiluminescent~~ indicators attached to said ~~one or more~~ nucleotides ~~or nucleotide analogs~~ .

Claim 1769 (CURRENTLY AMENDED). A process for determining the sequence of a nucleic acid of interest comprising ~~the steps of~~ :

generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof, wherein said fragments have been labeled by incorporation of one or more detectable non-radioactive modified or labeled nucleoside triphosphates ~~or analogs thereof~~ , said nucleoside triphosphates ~~or analogs~~ comprising fluorescent or chemiluminescent indicators;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting each of said separated or resolved fragments by means of the fluorescent or chemiluminescent indicators, to determine the sequence of said nucleic acid of interest.

Claim 1770 (CURRENTLY AMENDED). The process according to claim 1769, wherein in said generating step, said ~~one or more detectable non-radioactive~~ modified or labeled nucleoside triphosphates ~~or analogs thereof~~ comprise a sugar furanose moiety ~~or sugar analog~~.

Claim 1771 (CURRENTLY AMENDED). The process according to claim 1770, wherein said sugar furanose moiety ~~or sugar analog~~ comprises a ~~furanose selected from the group consisting of~~ ribose, deoxyribose, or dideoxyribose ~~and analogs thereof~~.

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

**Page 253 Amendment [Following Office Action of July 1, 2003] - December 31, 2003**

Claim 1772 (CURRENTLY AMENDED). The process according to claim 1769, wherein in said generating step, said one or more detectable non-radioactive modified or labeled nucleoside triphosphates ~~or analogs thereof~~ comprise a phosphate moiety ~~or a phosphate analog~~.

Claim 1773 (CURRENTLY AMENDED). The process according to claim 1769, wherein in said generating step, said ~~one or more detectable non-radioactive~~ modified or labeled nucleoside triphosphates ~~or analogs thereof~~ comprise a purine, a 7-deazapurine or a pyrimidine base moiety ~~or a base analog~~.

Claim 1774 (CURRENTLY CANCELLED). The process according to claim 1773, wherein said base moiety or base analog comprises a purine, a purine analog, a pyrimidine, or a pyrimidine analog.

Claim 1775 (CURRENTLY AMENDED). The process according to claim 1773, wherein the fluorescent or chemiluminescent indicators in said ~~one or more detectable non-radioactive~~ modified or labeled nucleoside triphosphates ~~or analogs thereof~~ are attached to said purine, 7-deazapurine or pyrimidine base moiety ~~or said base analog~~.

\* \* \* \* \*

Dean L. Engelhardt et al.

Serial No.: 08/486,069

Filed: June 7, 1995

Page 254 Amendment [Following Office Action of July 1, 2003] - December 31, 2003

### SUMMARY AND CONCLUSIONS

Applicant has filed herewith a Petition for a three-month extension of time with a request that the Patent and Trademark Office charge the fees due to Deposit Account No. 50-0206. Applicant believes that no additional fees are due. However, in the event that additional fees are due, Applicant hereby requests that the Patent and Trademark Office charge the amount of any such fees to Deposit Account No. 50-0206.

Presented for further prosecution on the merits are claims: 569-595, 597-605, 607, 608, 610-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-757, 759, 760, 762-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-909, 911, 912, 914-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1049, 1051, 1053-1061, 1063-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1170, 1172, 1173, 1175-1200, 1204, 1208-1210, 1212-1216, 1218-1250, 1252-1253, 1255-1258, 1261-1294, 1296-1329, 1331, 1332, 1334-1407, 1409-1488, 1490, 1491, 1493-1568, 1570-1612 and 1614-1616, 1618-1621, 1623-1628, 1631, 1632, 1635-1647, 1649-1773 and 1775.

If a telephone conversation would further prosecution of the application, the Examiner is welcome to call Applicant's undersigned attorney at the number below.

Respectfully submitted,  
HUNTON & WILLIAMS

Dated:

Dec 31, 2003

By:



Robert M. Schulman  
Registration No. 31,196  
Samson Vermont  
Registration No. 42,202

Hunton & Williams  
1900 K Street, NW, Suite 1200  
Washington, DC 20006  
T: (202) 955-1926  
F: (202) 778-2201